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Bisphenol A and cognitive function in school-age boys: Is BPA predominantly related to behavior?

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ABSTRACT

Background: Bisphenol A (BPA) has been associated with impairments in children's behavior, but few studies have investigated its relationship with cognitive function.
Objective: To investigate the association of urinary BPA concentrations with cognitive domains and intelligence quotient (IQ) in Spanish boys.
Methods: BPA levels were quantified by liquid chromatography-tandem mass spectrometry (LC–MS-MS) in one spot urine sample from 269 boys of the INMA-Granada cohort, in their follow-up at 9–11 years of age. Cognitive function was evaluated by a trained psychologist using a comprehensive neuropsychological test battery (including general intelligence, language skills, working memory, attention, impulsivity, visual-motor coordination, processing speed and executive function, among others). Cross-sectional associations between BPA levels and neuropsychological standardized scores were analyzed by adjusted linear and logistic regression models.
Results: Median (P25, P75) BPA concentrations were 4.76 (2.77, 9.03) μg/L and 4.75 (2.75, 10.2) μg/g of creatinine (Cr). Boys in the third and fourth quartile of volume-based BPA concentrations showed better processing speed scores than boys in the first quartile (β = 5.47; 95%CI: 1.4, 9.4 and β = 3.57; 95%CI: -0.4, 7.5, respectively); and boys in the third quartile showed better inhibitory control (β = 1.6; 95%CI: -0.3, 3.5) and impulsivity (β= -4.2; 95%CI: -9.0, 0.0). In contrast, boys in the fourth quartile showed poorer working memory scores than those in the first quartile (β= -1.0; 95%CI: -2.1, -0.1). All these associations were attenuated when Cr-standardized BPA concentrations were considered. Cr-based BPA concentrations were also associated with a higher risk of being below the 20th percentile of working memory scores [OR_a = 1.51; 95%CI: 1.01, 2.25].
Discussion: Our findings do not support an association between urinary BPA concentrations and cognitive function or IQ among boys, except for working memory. BPA was previously found to be associated with behavior problems in the same study population, suggesting that BPA may predominantly affect the behavior of children rather than their cognitive function, in line with previous epidemiologic studies.

1. Introduction

Bisphenol A (BPA) is a man-made chemical extensively used in the manufacture of a wide range of materials, including polycarbonate plastics, epoxy resin liners of canned food, medical devices, some dental sealants, and thermal receipts, among others (Vandenberg et al., 2007; Molina-Molina et al., 2019). Even more, BPA has recently been detected in socks for infants, highlighting the novel role of textiles as potential sources of chemical exposure (Freire et al., 2019). Diet is considered the predominant source of exposure to BPA in the general population, due its leaching from food packaging and can liners (Vandenberg et al., 2010), followed by dermal absorption and inhalation (Ehrlich et al., 2014; Michałowicz, 2014). Biomonitoring studies have confirmed the continuous and chronic exposure of humans to BPA, explaining its detection in the urine of more than 90% of the general population in Europe and the USA (Becker et al., 2009; Calafat et al., 2008; Casas

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et al., 2011; Vandenberg et al., 2010). BPA has been detected in other biological matrices besides urine, such as maternal blood, placenta, amniotic fluid, cord and fetal serum blood, and maternal breast milk, demonstrating the internal exposure to BPA of mothers, fetuses, and newborns (Vandenberg et al., 2010).

BPA is a known endocrine-disrupting compound (EDC) with the potential to alter hormonal homeostasis (Mustieles et al., 2018a), even at environmentally relevant doses, through its effects on multiple steroid hormone receptors that mediate a myriad of cellular effects (Casals-Casas and Desvergne, 2011; Vandenberg et al., 2010). Several in vitro and in vivo studies have shown that BPA can interfere with estrogenic pathways by binding to nuclear estrogen receptors (ERs) (Wetherill et al., 2007) as well as other membrane estrogen receptor families (Alonso-Magdalena et al., 2012). It has also been found to exert antagonistic activities after binding to the androgen receptor (Molina-Molina et al., 2013) and to alter the expression of steroidogenic enzymes, as well as interacting with glucocorticoid, PPAR-γ, and thyroid signaling pathways (Mustieles et al., 2015, 2018b).

The developing brain is a key target for BPA, and experimental studies have associated pre-, peri, and post-natal BPA exposure with various alterations in brain structure, behavior, and certain cognitive domains (Nesan et al., 2018). Rodent models have shown that BPA can alter the expression of nuclear estrogen receptors in the amygdala and hypothalamus (Cao et al., 2013; Rebuli et al., 2014), in neuronal cell populations in the substantia nigra (Tando et al., 2007), in the periventricular preoptic area of the hypothalamus (Rubin et al., 2006), and in the locus coeruleus (Tando et al., 2014). Behavioral changes linked to BPA exposure include increased anxiety (Luo et al., 2014; Xu et al., 2012), hyperactivity (Komada et al., 2014), greater aggressiveness (Patisaul and Bateman, 2008), and modifications in socio-sexual (Porrini et al., 2005) and play (Dessì-Fulgheri et al., 2002) behaviors. Rodent studies have also found that BPA exposure induces spatial and non-spatial memory impairments associated with neural modifications, especially in processes involved in synaptic plasticity (Kuwahara et al., 2013; Mhaouty-Kodja et al., 2018; Poimenova et al., 2010; Weinberger et al., 2014; Xu et al., 2010).

Although most published studies have analyzed the relationship of developmental BPA exposure with the behavior of children, which has been reported to be sex-specific (Casas et al., 2015; Findlay and Kohen, 2015; Mustieles et al., 2015, 2018b; Perera et al., 2012; Roen et al., 2015), much less is known about its relationship with their cognitive functions. Therefore, the objective of this study was to explore the relationship of urinary BPA concentrations with cognitive functioning in a group of Spanish boys aged 9–11 years.

2. Methods

2.1. Study population

The INMA (Infancia y Medio Ambiente – Environment and Childhood) cohort is a population-based study developed in seven Spanish regions with the aim of exploring the possible effects of environmental pollutants during pregnancy and early childhood (Guxens et al., 2012) on child growth and development. From 2000 to 2002, the INMA-Granada sub-cohort enrolled 668 mother-son pairs (Fernandez et al., 2007). For the current study, all families from the INMA-Granada cohort were contacted and invited to participate in the 2010–2012 follow-up, when the children reached the age of 9–11 years. Written consent was obtained from 300 families (44.9%), and BPA concentrations were available for 298 boys. Eighteen of these children were excluded from the present study for the presence of chronic disease that could interfere with cognitive development, i.e., hyperthyroidism (n = 1), diabetes (n = 1), language disorder (n = 2), attention deficit hyperactivity disorder (ADHD) (n = 7), Noonan syndrome (n = 1), Asperger syndrome (n = 2), cerebral palsy (n = 1), Tourette syndrome with ADHD (n = 1), and Charcot–Marie–Toth syndrome with ADHD (n = 1), and for a history of brain tumor surgery (n = 1). Additionally, 11 children were excluded due to an incomplete neuropsychological assessment or the absence of important covariate data. Therefore, the final study sample size comprised 269 mother-son pairs with data available on urinary BPA concentrations, cognitive assessment data, and covariates. The study followed the principles of the declaration of Helsinki and was approved by the Ethics Committee of San Cecilio University Hospital (Granada, Spain).

2.2. BPA exposure assessment

At the follow-up session at the hospital, always held between 5 p.m. and 8 p.m., a single non-fasting spot urine sample was collected in a 10-mL polypropylene tube and immediately stored at -20 °C. Total BPA (free plus conjugated) was quantified at the laboratory of the Analytical Chemistry Department of Cordoba University (Spain) as previously described (Perez-Lobato et al., 2016), using liquid chromatography-mass spectrometry with a limit of detection (LOD) of 0.1 μg/L and a limit of quantification (LOQ) of 0.2 μg/L. Urinary creatinine (Cr) concentrations (mg/dl) were determined at the Public Health Laboratory of the Basque Country (Spain) to account for urine dilution (Fernández et al., 2015). The researchers who conducted the urine analyses were blinded to the characteristics of the study participants. Collection, storage, and processing of urine samples were conducted under controlled conditions, and account was taken of background BPA contamination from the presence of polymers in components of the urine collection containers and/or equipment or labware. An inter-laboratory comparison was also performed with the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA)—Institute of the Ruhr-University Bochum (Germany), with considerable experience in BPA determination.

2.3. Neuropsychological assessment

The cognitive function of each boy was assessed at the University Hospital facilities by a trained neuropsychologist (RPL) blinded to their exposure levels, using a comprehensive neuropsychological battery of tests (Perez-Lobato et al., 2015). This battery was chosen because it assesses omnibus features of child neurodevelopment (e.g., IQ, language, attention, processing speed, etc.) and because previous epidemiologic studies have used similar tests to study cognitive domains in relation to BPA exposure (Mustieles et al., 2015):

1 **General cognitive intelligence:** applying the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 1997) and basing the IQ calculation on verbal and nonverbal scale scores.
2 **Language:** using the verbal scale of the K-BIT (Kaufman and Kaufman, 1997), which has two subtests: i) verbal knowledge, in which the child must name graphically displayed objects to assess receptive vocabulary; and ii) general knowledge and riddles, in which the child must name words from their definition and their visualization with letters missing to assess expressive reasoning.
3 **Attention:** applying the continuous performance test (CPT) (Conners, 1995) to assess sustained and selective attention together with impulsivity. In this task, the child must press any key on the keyboard as quickly as possible whenever the letter 'A' appears in yellow ('go' condition). Dependent variables for analyses are hits (press any key in 'go' condition), commission errors (press any key in 'no go' condition), omission errors (no key pressed in 'go' condition), and attention index.
4 **Verbal memory:** applying the Complutense-Spain Madrid verbal learning test (TAVECI) (Benedet et al., 2001) to assess different memory and learning processes, including immediate recall, short- and long term recall, and recognition. The examiner reads aloud a list of 15 words five times. The child must state words recalled immediately after each reading and then after intervals of 10 and

20 min.

5 **Visual-motor coordination:** applying the Trail Making Test part A (TMTA) (Reitan, 1958), in which the child must connect consecutive numbers in an alternating sequence as quickly as possible, with the time in seconds (s) as dependent variable.

6 **Processing speed:** calculating the sum of two subtests (symbol search and coding) from Edition IV of the Wechsler Intelligence Scales for Children (WISC-IV) (Wechsler, 2007). The two tasks must be completed in a maximum of 2 min. In the first task, the child selects certain figures from a series of figures. In the second task, the child fills in spaces under numbers with corresponding symbols following an established model.

7 **Executive function:** assessing four components: updating, inhibition, shifting, and abstract reasoning (Diamond, 2013).

8 **Updating measurements:** assessing two components: a) Working memory: the child listens to a letter–number sequencing subtest from the WISC-IV (Spanish version) and repeats the numbers from the lowest to the highest, followed by repetition of the letters in alphabetic order (Wechsler, 2007); b) Verbal fluency: the children must say as many names of animals as possible during a 1-min period in the categorical verbal fluency test (FAS), with the number of animals correctly pronounced as dependent variable (Benton and Hamsher, 1989).

9 **Inhibition:** applying two subtests: a) the Spanish version of the Stroop Color and Word Test (Golden, 2005) to evaluate cognition and inhibition, in which the child must name colored words (condition 1), read color-words printed in black ink (condition 2), and name the color of words printed in colors that conflict with their meaning, e.g. the word 'red' appears in yellow ink (condition 3, inhibition); the dependent variable is the interference score, calculated from the results of the three conditions using a specific formula; b) the Go/No-Go task (Donders, 1969) to evaluate motor inhibition, in which the child must respond to certain stimuli on the computer screen while inhibiting any response to a distracter stimulus, with the hit and false alarm rates as dependent variables.

10 **Shifting:** using part B of the TMT (Reitan, 1958), in which the child must connect consecutive numbers and letters in an alternating sequence as quickly as possible, with the time measured in seconds (s) as dependent variable.

11 **Abstract reasoning (matrix analogies test):** measured with the non-verbal scale of the K-BIT (Kaufman and Kaufman, 1997). The child selects a picture that best completes a visual pattern following a visual analogy. The dependent variable is the number of correct responses.

A higher score always indicates better cognitive function except for the following tests, in which a higher score indicates worse cognitive function: i) subtests "*commission errors*" and "*omissions*" from the *CPT* test on sustained attention function; ii) *the TMT-A* test of visual-motor coordination function; iii) the *TMT-B* test of shifting; and iv) the "*false-alarm rate*" subtest of the Go/No-Go test on impulsivity and/or inhibition function.

2.4. Covariates

Models were adjusted for the same set of covariates as in a previous study of BPA and behavior in the same population (Perez-Lobato et al., 2016), including: breastfeeding and smoking during pregnancy; child's age and body mass index [BMI (kg/m^2)] (Wirt et al., 2015), and mother's age, marital status (married/not married), education level (university/secondary school/up to primary) and mother's intelligence score, measured with the Similarities subtest of the Wechsler Adult Intelligence-Third Edition (WAIS-III) at the time of assessment. The final models also included as potential confounders exposure to environmental tobacco smoke (any/none) in the home, based on questionnaire.

2.5. Statistical analysis

The analysis was based on our previous experience of behavior and cognitive functioning in these same children from the INMA-Granada cohort (Pérez-Lobato et al., 2015 and 2016). In the descriptive analysis of parental and children characteristics, absolute frequencies were calculated for categorical variables, and measures of central tendency and dispersion for continuous variables. The relationship of urinary BPA concentrations with the characteristics of children and parents was analyzed with the Mann–Whitney or Kruskal–Wallis test for categorical covariates and the Spearman correlation test for continuous covariates.

The median value and interquartile range (IQR) of BPA concentrations (μg/L) were calculated. BPA exposure was considered using both volume-based urinary BPA (μg/L) and creatinine (Cr)-standardized urinary BPA (μg/g) concentrations, as independent variables, as recommended (LaKind and Naiman, 2015). These concentrations were $\log_e$-transformed to standardize the data distribution and reduce the influence of outliers. BPA levels were also divided into quartiles to evaluate potential non-linear associations. Mean (standard deviation), median and range values were calculated for neuropsychological test scores, which were analyzed as continuous variables because some scores could not be standardized for Spanish child populations.

Linear regression models were used to analyze the association between BPA concentrations and neuropsychological test scores, with Beta coefficients representing the mean change in neuropsychological scores associated with each unit increase in $\log_e$-BPA concentrations or the mean difference in neuropsychological scores between the second, third, or fourth quartiles and the first quartile of BPA exposure. Their respective 95% Confidence Intervals (CIs) were also calculated. Logistic regression models were also performed using $\log_e$-transformed Cr-standardized BPA concentrations to analyze the risk of being below or above the 20th or 80th percentile of cognitive function scores, calculating multivariable-adjusted odds ratios (ORs) with their corresponding 95% CIs. All models were adjusted for children's age and BMI, tobacco exposure at home, mothers' age, intelligence, marital status, education level, breastfeeding, and smoking during pregnancy.

SPSS v20.0 (IBM, Chicago, IL) was used for data analyses, and the significance level was set at $p \leq 0.05$.

3. Results

3.1. Characteristics of the study population

The mean (± standard deviation) age of the children was 9.9 (± 0.3) years, the mean BMI 19.2 (± 3.5) kg/m^2, and around one-third of families reported tobacco exposure at home (Table 1). The median age was 39.7 (± 4.9) years for mothers and 42.1 (± 5.4) years for fathers; 23.4% of mothers and 21.6% of fathers had completed university education, around 90% of mothers and fathers were married, 21.6% of mothers reported smoking during pregnancy, and 87% reported breastfeeding the child. The place of residence was urban in 24.5% of families, semirural in 58%, and rural in 17.5% (Table 1).

BPA was found in all urine samples, at a wide range of concentrations. Fig. 1 shows a boxplot of BPA concentrations. Median (P25, P75) urinary BPA concentrations (μg/L) and Cr-standardized BPA concentrations (μg/g) were 4.76 (2.77, 9.03) and 4.75 (2.75, 10.2), respectively. Table 2 displays the distribution of the raw cognitive function scores of the children. Median IQ was 108 and all remaining cognitive scores were within normal ranges.

3.2. Cross-sectional associations between BPA and cognitive function scores

When $\log_e$-transformed volume-based urinary BPA concentrations (μg/L) were used as a continuous variable, higher BPA levels tended to be associated with greater cognitive function scores, although in general, confidence intervals included the null value. In adjusted models,

Table 1
Geometric mean and 'geometric mean standard deviation' of urinary BPA concentrations (μg/L) by demographic characteristics of the study population (n = 269).

	n	Mean (SD)/%	BPA (μg/L) Median	GM ± GSD	*p* Value[1]
Child Variables					
Age (years)	269	9.9 (0.3)	–	–	0.08
BMI (kg/m^2)	269	19.2 (3.5)	–	–	0.93
Urinary creatinine (mg/dL)	269	90.2 (0.5)	–	–	0.07
IQ	269	108.2 (11.8)	–	–	0.15
Area of residence (%)					
Urban	269	24.5	5.2	4.7 ± 2.7	0.66
Semiurban	269	58.0	4.7	4.7 ± 2.5	
Rural	269	17.5	4.4	4.2 ± 2.8	
Tobacco Exposure (%)					
Yes	269	29.4	4.7	4.7 ± 2.5	0.85
No	269	70.6	4.8	4.4 ± 2.8	
Maternal Variables					
Age (years)	269	39.7 (4.9)	–	–	0.55
Verbal reasoning[2]	269	14.9 (4.6)	–	–	0.76
Marital status (%)					
Married	269	90.7	4.7	4.6 ± 2.5	0.57
Unmarried	269	9.3	5.2	4.6 ± 3.2	
Education Level (%)					
University	269	23.4	5.0	5.2 ± 2.7	0.26
Secondary school	269	31.6	5.0	4.8 ± 2.3	
Up to primary	269	45.0	4.13	4.2 ± 2.7	
Breastfeeding (%)					
Yes	269	87.0	4.7	4.6 ± 2.5	0.88
No	269	13.0	5.1	4.6 ± 3.5	
Smoking during pregnancy[3] (%)					
Yes	269	21.6	4.9	4.7 ± 2.6	0.85
No	269	78.4	4.7	4.6 ± 2.6	
Paternal Variables					
Age (years)	262	42.1 (5.4)	–	–	0.42
Marital status (%)					
Married	263	90.3	4.7	4.6 ± 2.5	0.62
Unmarried	263	9.7	5.1	4.6 ± 2.7	
Education level (%)					
University	266	21.6	4.3	4.2 ± 2.7	0.30
Secondary school	266	32.0	5.0	5.5 ± 2.5	
Up to primary	266	45.4	4.8	4.3 ± 2.6	

GM: geometric mean; GSD: geometric standard deviation; SD = standard deviation; IQ: intelligence quotient.

[1] *p*-Value: Statistical significance value reached for hypothesis testing (Mann-Whitney test for breastfeeding, smoking during pregnancy, Kruskal–Wallis test for area of residence, maternal and paternal education. Finally, for continuous variables, bivariate analysis with Spearman correlation test).

[2] Verbal reasoning, measured by Similarities subtest of WAIS-III.

[3] Mother's habit.

higher BPA concentrations were associated with lower impulsivity [β = -1.70; 95%CI: -3.36, -0.05], faster processing speed [β = 1.57; 95%CI: 0.09, 3.04], and better inhibitory control [β = 0.75; 95%CI: 0.06, 1.43] (Table 3). However, when $\log_e$-transformed Cr-standardized urinary BPA concentrations (μg/g) were used as continuous variable, adjusted models showed an attenuation of previous associations towards impulsivity [β = -1.67; 95%CI: -3.32, -0.00], processing speed [β = 1.29; 95%CI: -0.20, -2.77], and inhibitory control [β = 0.61; 95%CI: -0.08, 1.30] (Table 4).

When volume-based urinary BPA concentrations were categorized in quartiles, the processing speed was faster for boys in the third and fourth quartile of BPA concentrations than for those in the first quartile [third quartile β = 5.47; 95%CI: 1.4, 9.4; fourth quartile β = 3.57; 95%CI: -0.4, 7.5], while boys in the third quartile showed better inhibitory control [third quartile β = 1.6; 95%CI: -0.3, 3.5] and impulsivity [third quartile β = -4.2; 95%CI: -9.0, 0.0] (Table 5). In contrast, boys in the fourth quartile showed worse working memory than those in the first quartile [fourth quartile β = -1.0; 95%CI: -2.1, -0.1]. All these associations were attenuated when quartiles of Cr-standardized BPA concentrations were considered (Table 5).

Logistic regression analyses also showed that higher loge-transformed Cr-standardized BPA concentrations were associated with a higher risk of being below the 20th percentile of working memory, in both unadjusted and adjusted models [OR = 1.44; 95%CI: 1.00, 2.08; OR a = 1.51; 95%CI: 1.01, 2.25]. No associations were observed with the remaining cognitive functions evaluated (Table 6).

4. Discussion

The results of this study do not support a relationship between urinary BPA concentrations and cognitive abilities in boys at 9–11 years of age. Initially, some associations were observed with specific cognitive functions, but these were attenuated or disappeared when the models were adjusted for covariates or when Cr-standardized BPA concentrations were considered, with the exception of working memory. Given the comprehensive assessment of neuropsychological functions conducted, the absence of associations is surprising, especially in the context of previous associations found with behavior throughout the literature (Mustieles et al., 2015).

A previous study of the same study population, including the same 269 boys as in the current analysis, found that higher volume-based and Cr-standardized BPA concentrations were both associated with worse behavioral scores in all scales, mainly with more somatic complaints and more social and thought problems, and that there were no substantial differences between unadjusted and adjusted models (Perez-Lobato et al., 2016). In contrast, no consistent associations were observed between urinary BPA concentrations and cognitive functions in the present study, even when models were adjusted for the same set of covariates, except for a potential association between higher BPA concentrations and poorer working memory.

Our findings are in line with previous epidemiological studies on child behavior and cognitive functions, suggesting that BPA exposure may be predominantly associated with behavior domains rather than cognitive functions. Although epidemiologic evidence on the impact of BPA exposure in children has been strengthened over the past few years, most researchers have assessed behavior rather than cognitive function. Moreover, the few studies on cognitive function have published less consistent results than those obtained for children's behavior (Ejaredar et al., 2017; Mustieles et al., 2015, 2018b). Thus, in the EDEN birth cohort, Philippat et al. (2017) reported the association of prenatal urinary BPA concentrations with relationship problems and hyperactivity–inattention in children at 3 and 5 years of age (Philippat et al., 2017). In the same cohort, Nakiwala et al. (2018) found no association in the boys between prenatal BPA exposure and the verbal performance or IQ (Nakiwala et al., 2018) (see Supplemental Table 1). A similar pattern was observed in the Spanish INMA-Sabadell cohort, in which prenatal BPA exposure was associated with an increased risk of ADHD-hyperactivity symptoms and psychomotor development but not with cognitive development (Casas et al., 2015). Likewise, in a study of the MIREC mother-child cohort (Braun et al., 2017a), higher prenatal urinary BPA concentrations were related to more behavior problems in the children at 3 years of age, but no significant associations were found with most of cognitive functions (Braun et al., 2017a). Finally, exposure to dental composite restorations based on bisphenol A-glycidyl methacrylate was associated with behavior problems but not cognitive functions in the New England Children's Amalgam Trial (NECAT) of children aged 6–10 years (Maserejian et al., 2012a, b; Maserejian et al., 2014). Further details of these epidemiological studies are summarized in Supplemental Table 1.

Prenatal urinary BPA concentrations have been consistently

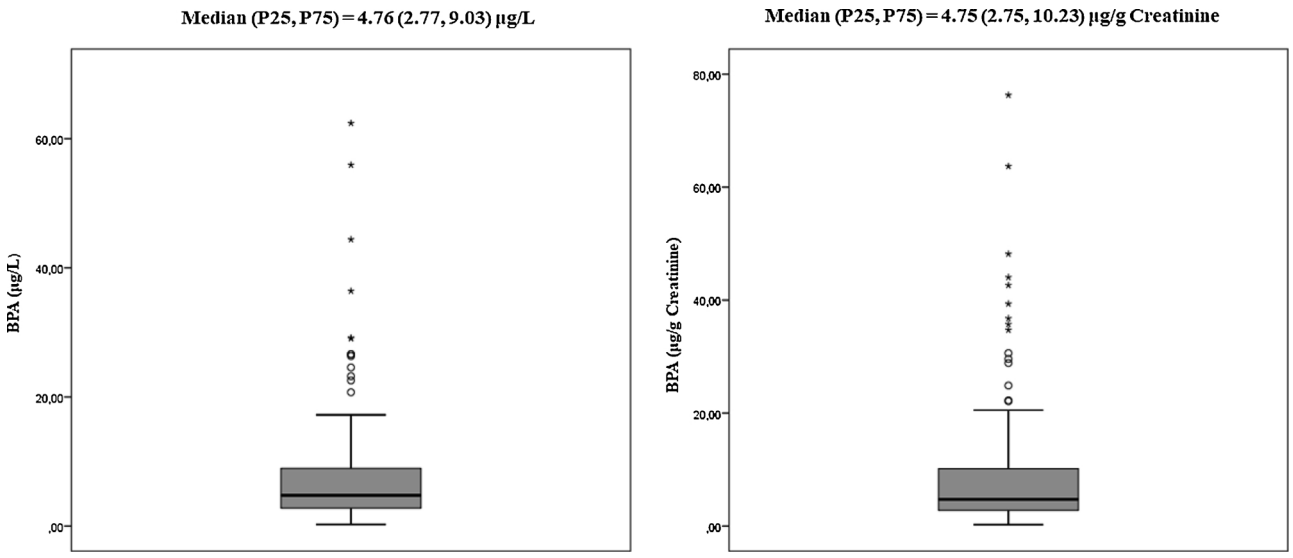

Fig. 1. Boxplots of urinary BPA concentrations (µg/L) and urinary creatinine-adjusted BPA (µg/g) in 269 boys from the INMA-Granada cohort.

associated with more behavior problems and worse executive function during infancy, persisting into early and late childhood among children from the HOME cohort Study (Braun et al., 2011, 2017b; Stacy et al., 2017). However, prenatal BPA exposure has not been associated with any specific cognitive domain or with the IQ over time (Braun et al., 2017a; Stacy et al., 2017). Only BPA exposure was cross-sectionally associated with worse overall cognition, verbal abilities and speed of mental processing among boys in the HOME study at 8 years of age (Stacy et al., 2017), and only working memory, a component of executive function, remained negatively and significant associated with BPA exposure among boys in the MIREC study at 3 years of age (Braun et al., 2017a). Another exception is the association of higher prenatal urinary BPA concentrations with a greater risk of poorer language skills among male but not female toddlers in the Odense Child Cohort,

Table 2
Children's scores in neuropsychological tests.

Cognitive Function	Test	n	Median	Mean	SD	Range
General Cognitive	IQ[b]	269	108.0	108.2	11.8	77 to 141
Verbal expression and comprehension	K-BIT					
	Full verbal[b]	269	52.0	51.2	5.5	32 to 73
Sustained attention	CPT					
	Correct detection[b]	258	65.0	63.7	5.7	35 to 70
	Commission errors[c]	258	7.0	9.6	11.6	0 to 110
	Omissions[c]	258	5.0	6.4	5.6	0 to 35
	Attention Index[b]	258	1.0	0.7	0.4	0 to 1
Verbal Memory	TAVEC					
	Immediate Recall Trial 1[b]	269	7.0	7.0	1.7	3 to 12
	Immediate Recall Trial 5[b]	269	12.0	11.9	2.1	6 to 15
	Short-term recall[b]	269	11.0	11.0	2.4	4 to 15
	Long-term recall[b]	269	12.0	11.5	2.5	4 to 15
Visual-motor coordination	TMT-A time (s)[c]	268	27.0	29.0	10.8	9 to 86
Processing speed	WISC-IV					
	Verbal Performance[b]	268	99.0	97.5	11.4	64 to 130
Executive Functions						
Working Memory	WISC-IV					
	Letter-number sequencing[b]	269	17.0	17.4	2.7	10 to 25
Verbal Fluency	FAS[b]	267	17.0	17.0	4.2	6 to 28
Impulsivity/Inhibition	STROOP					
	Words[b]	267	114.0	113.9	10.3	86 to 141
	Colors[b]	267	79.0	79.2	9.0	55 to 109
	Words and Colors[b]	267	49.0	48.6	7.0	30 to 71
	Inhibitory Control (Interference)[b]	267	2.0	2.2	5.3	−16.7 to 20.8
	GO NO GO					
	Hit rate[b]	255	1.0	1.0	0.04	0.5 to 1.0
	False-alarm rate[c]	255	0.05	0.06	0.59	0.00 to 0.39
Shifting	TMT-B time (s)[c]	268	53.0	60.1	31.8	23 to 360
Abstract reasoning	Matrix analogies[b]	269	31.0	31.1	4.7	18 to 44

CPT = Continuous performance test; FAS = Verbal fluency test; IQ = Intelligence quotient; K-BIT = Kaufman brief intelligence test; SD = Standard deviation; s = seconds; STROOP = Stroop color and word test; TAVECI = Complutense-Spain Madrid verbal learning test; TMT = Trail making test; WISC-IV = Wechsler Intelligence Scale for Children;

[a]For all tests, direct scores were used in the analysis.

[b] Higher scores determines better cognitive function.

[c] Higher score determines worse cognitive function.

Table 3
Distribution of cognitive function scores by log_e BPA (μg/L) concentrations among 269 boys from the INMA-Granada cohort.

Cognitive Functions		BPA (log_e transformed, unadjusted for covariates)		BPA (log_e transformed, adjusted for covariates[e])	
	n	β	95%CI	β	95% CI
Intelligence quotient (IQ)[b]	269	1.13	−0.36;2.62	0.21	−1.26; 1.69
Verbal comprehension[b]	269	0.31	−0.39;1.01	0.16	−0.57; 0.89
Impulsivity[c]	258	−1.39	−2.87;0.09†	−1.70	−3.36; -0.05*
Attention Index[b]	258	−0.03	−0.09;0.02	−0.04	−0.10;0.02
Long-term recall[b]	269	−0.01	−0.32;0.31	−0.14	−0.47;0.20
Immediate Recall Trial 5[b]	269	0.01	−0.26;0.27	−0.13	−0.41; 0.15
Visual-motor coordination (s)[c]	268	0.17	−1.20:1.54	0.33	−1.10; 1.77
Processing speed[b]	268	1.57	0.13;3.01*	1.57	0.09;3.04*
Working Memory[b]	269	−0.05	−0.40;0.29	−0.25	−0.61;0.11
Verbal Fluency[b]	267	0.18	−0.34;0.71	0.21	−0.35;0.76
Inhibitory Control (Interference)[b]	267	0.65	−0.18;1.32†	0.75	0.06;1.43*
Hit rate[b]	255	0.00	−0.00;0.01	0.00	−0.00;0.01
False-alarm rate[c]	255	−0.00	−0.01;0.01	−0.00	−0.01;0.00
Shifting (s)[c]	268	−0.99	−5.03;3.05	−2.12	−5.76;1.52
Abstract reasoning[b]	269	0.28	−0.36;0.87	0.01	−0.58;0.60

CI: confidence interval; s = seconds. * p ≤ 0.05; † p ≤ 0.1.
[a]We show the most relevant abilities measured. For all tests, direct scores were used in the analysis.
[b]A higher score indicates better cognitive function.
[c]A higher score indicates worse cognitive function.
[d]Immediate Recall Trial 5 (TAVECI).
[e]Models were adjusted for child's age (years), BMI (kg/m^2), smoking exposure at home (yes/no), mother's age at time of assessment (years), mother's intelligence score, maternal marital status (married/unmarried), maternal education (university/secondary school/up to primary), smoking exposure during pregnancy (yes/no) and breastfeeding (yes/no).

Table 4
Distribution of cognitive function scores by log_e BPA Cr-standardized (μg/g) concentrations among 269 boys from the INMA-Granada cohort.

Cognitive functions[a]		BPA/Creatinine (μg/g) (log_e transformed, unadjusted for covariates)		BPA/Creatinine (μg/g) (log_e transformed, adjusted for covariates[e])	
	n	β	95% CI	β (SE)	95% CI
Intelligence quotient (IQ)[b]	269	0.55	−0.94;2.03	−0.07	−1.54;1.41
Verbal comprehension[b]	269	0.09	−0.60;0.80	0.16	−0.58;0.89
Impulsivity[c]	258	−1.30	−2.77;0.18†	−1.67	−3.32; -0.00*
Attention Index[b]	258	−0.03	−0.09;0.03	−0.04	−0.10;0.03
Long-term recall[b]	269	−0.02	−0.33; 0.30	−0.18	−0.51;0.15
Immediate Recall Trial 5[b]	269	0.06	−0.21;0.32	−0.10	−0.38;0.18
Visual-motor coordination (s)[c]	268	0.08	−1.28;1.44	−0.00	−1.44;1.44
Processing speed[b]	268	1.31	−0.12;2.75†	1.29	−0.20;2.77†
Working Memory[b]	269	−0.07	−0.41;0.27	−0.20	−0.56;0.16
Verbal Fluency[b]	267	0.17	−0.36;0.70	0.28	−0.28;0.84
Inhibitory Control (Interference)[b]	267	0.48	−0.19;1.14	0.61	−0.08;1.30†
Hit rate[b]	255	0.00	−0.00;0.01	0.00	−0.00;0.01
False-alarm rate[c]	255	−0.00	−0.01;0.00	−0.01	−0.01;0.00
Shifting (s)[c]	268	−0.07	−4.08;3.94	−1.44	−5.10;2.21
Abstract reasoning[b]	269	−0.09	−0.68;0.50	−0.18	−0.77;0.41

SE = standard error; CI: confidence interval; s = seconds. * p ≤ 0.05; † p ≤ 0.1.
[a]We show the most relevant abilities measured. For all tests, direct scores were used in the analysis.
[b]A higher score indicates better cognitive function.
[c]A higher score indicates worse cognitive function.
[d]Immediate Recall Trial 5 (TAVECI).
[e]Models were adjusted for child's age (years), BMI (kg/m^2), smoking exposure at home (yes/no), mother's age at time of assessment (years), mother's intelligence score, marital status (married/unmarried), maternal education (university/secondary school/up to primary), smoking exposure during pregnancy (yes/no) and breastfeeding (yes/no).

suggesting a possible sex-specific effect of BPA on early language development, although no association was found with ADHD symptoms (Jensen et al., 2019).

Differences in findings on the effects of BPA exposure between children's behavior and their cognitive functions may in part be attributable to methodological factors. Thus, trained psychologists usually conduct the assessment of cognitive function at a specific time point, whereas the parents report on the behavior of their children in daily life. It is also possible that sex-specific behaviors may be more sensitive to BPA exposure in comparison to cognitive domains and the IQ, which may also explain the different patterns described in the literature (Mustieles et al., 2015, 2018b). In general, the relationship of BPA exposure to behavior problems rather than cognition appears to be a consistent pattern in the epidemiologic literature, although further studies on cognition are required.

Experimental studies, mostly in rodents, have shown that BPA exposure can interfere with diverse brain areas and functions, leading not only to behavioral changes but also to impairments in memory and spatial learning, among other functions (Braun et al., 2017c; Gore et al., 2018). These results could be at least partially explained by hormonal mechanisms related to an altered estrogen-androgen balance (Mustieles et al., 2015). These include subtle epigenetic disruptions of nuclear estrogenic receptors and developmental alterations in sexually-dimorphic brain areas and functions in response to low BPA doses, as shown in the CLARITY-BPA studies, among others (Arambula et al., 2018, 2017,2016; Kundakovic et al., 2013). A recent review of the CLARITY-BPA studies confirms this altered neuroendocrine development, and the abrogation of brain and behavioral sexual dimorphisms, even at BPA doses below those considered "safe" for humans by regulatory agencies (Patisaul, 2019).

The median urinary BPA concentration in this study was 4.75 μg/L (4.76 μg/g Cr), similar to some previous findings in children of the same age (Calafat et al., 2008) and younger populations (Braun et al., 2011; Casas et al., 2011; Perera et al., 2012); however, it was higher than observations in other studies of children of the same age, including: the German Environmental Survey on Children (Becker et al., 2009), 2.13 ng/mL; the 2005–2006 NHANES study (Lakind and Naiman, 2011), 2.7 ng/mL, the 2007–2011 Canadian Health measures survey

Table 5
Distribution of cognitive function scores by quartiles of urinary bisphenol A and Cr-standardized bisphenol A concentrations among 269 boys from the INMA-Granada cohort.

		BPA Quartiles (μg/L)				BPA/creatinine quartiles (μg/g)			
Cognitive functions[a]	n	Reference Scores	Coefficients (CIs)			Reference Scores	Coefficients (CIs)		
		Mean (SD) (0.3-2.8 μg/L)	2nd (2.8-4.5 μg/L)	3rd (4.8-8.9 μg/L)	4th (9.1-62.4 μg/L)	Median (SD) (0.3-2.8 μg/g)	2nd (2.8–4.8 μg/g)	3rd (4.8-10.2 μg/g)	4th (10.3-76.3 μg/g)
Intelligence quotient (IQ)[b]	269	107.0 (11.5)	−0.3 (-4.3;3.8)	−1.0 (-4.7;3.3)	1.2 (-2.7;5.2)	106.9 (10.81)	−0.3 (-4.2;4.0)	−0.6 (-4.4;3.6)	0.7 (-3.1;4.9)
Verbal comprehension[b]	269	51.0 (6.3)	−0.3 (-2.3;1.7)	−0.1 (-1.9;2.0)	0.6 (-1.4;2.6)	50.9 (5.9)	−0.0 (-2.0;2.1)	−0.2 (-2.1;1.9)	0.7 (-1.2;2.8)
Attention									
Impulsivity[c]	258	11.7 (18.5)	−1.6 (-6.3;2.9)	−4.2 (-9.0;0.0)†	−3.2 (-7.7;1.2)	12.0 (16.0)	−2.2 (-7.0;2.2)	−4.1 (-8.9;0.1)†	−4.0 (-8.6;0.4)†
Attention Index[b]	258	0.8 (0.4)	−0.1 (-0.2;0.1)	−0.1 (-0.3;0.1)	−0.1 (-0.3;0.0)	0.8 (0.4)	−0.1 (-0.2;0.1)	−0.1 (-0.3;0.1)	−0.1 (-0.3;0.1)
Verbal Memory									
Long-term recall[b]	269	11.3 (2.6)	0.1 (-0.8;1.0)	0.0 (-0.9;0.9)	−0.5 (-1.4;0.4)	11.4 (2.4)	−0.3 (-1.3;0.5)	−0.4 (-1.3;0.5)	−0.4 (-1.4;0.4)
Immediate Recall Trial 5[b]	269	11.8 (2.1)	−0.4 (-1.3;0.5)	−0.4 (-1.2;0.5)	−0.6 (-1.4;0.3)	11.8 (2.1)	−0.2 (-1.3;0.4)	−0.2 (-1.2;0.5)	−0.2 (-1.3;0.4)
Visual-motor coordination[c]	268	28.7 (10.7)	0.0 (-3.9;4.0)	1.0 (-2.6;5.1)	0.8 (-3.0;4.7)	28.7 (10.9)	0.3 (-3.5;4.5)	1.3 (-2.3;5.5)	−0.1 (-3.7;4.1)
Processing speed[b]	268	94.9 (11.6)	2.3 (-1.8;6.3)	5.4 (1.4;9.4)*	3.5 (-0.4;7.5)†	96.7 (11.0)	−0.3 (-4.5;3.7)	1.1 (-3.1;5.0)	2.5 (-1.7;6.4)
Executive Function									
Working Memory[b]	269	17.6 (2.2)	−0.4 (-1.4;0.6)	−0.5 (-1.5;0.5)	−1.0 (-2.1;-0.1)*	17.4 (2.2)	−0.2 (-1.3;0.7)	0.0 (-1.0;1.0)	−0.6 (-1.6;0.3)
Verbal Fluency[b]	267	16.6 (3.9)	0.3 (-1.2;1.9)	0.0 (-1.5;1.6)	0.7 (-0.9;2.2)	16.5 (3.7)	0.3 (-1.2;1.9)	0.5 (-1.0;2.0)	0.6 (-0.9;2.1)
Impulsivity/Inhibition									
Inhibitory Control (Interference)[b]	267	1.4 (4.7)	0.1 (-1.8;2.0)	1.6 (-0.3;3.5)†	1.6 (-0.3;3.4)	1.7 (4.3)	0.4 (-1.5;2.4)	1.0 (-0.8;3.0)	0.7 (-1.2;2.6)
Hit rate[b]	255	1.0 (0.7)	0.0 (-0.0;0.0)	0.0 (-0.0;0.0)	0.0 (-0.0;0.0)	1.0 (0.1)	0.0 (-0.0;0.0)	0.0 (-0.0;0.0)	0.0 (-0.0;0.0)
False-alarm rate[c]	255	0.1 (0.1)	−0.0 (-0.0;0.0)	−0.0 (-0.0;0.0)	−0.0 (-0.0;0.0)	0.1 (0.1)	−0.0 (-0.0;0.0)	−0.0 (-0.0;0.0)	−0.0 (-0.0;0.0)
Shifting[c]	268	63.4 (27.9)	−8.3 (-18.2;1.7)	−5.5 (-15.4;4.4)	−1.7 (-11.5;8.2)	62.5 (25.3)	−5.6 (-15.8;4.5)	−2.2 (-12.0;7.8)	−3.0 (-12.9;7.0)
Abstract reasoning[b]	269	30.8 (4.2)	0.3 (-1.3;1.9)	−0.5 (-2.1;1.2)	0.3 (-1.3;1.9)	31.0 (3.9)	−0.3 (-1.9;1.4)	−0.2 (-1.8;1.4)	−0.2 (-1.7;1.5)

CI: confidence interval; SD = standard deviation.
Linear regression models were adjusted for child's age, BMI (kg/m2), and exposure to environmental tobacco smoke (yes/no) in the home based on questionnaire, mother's age at the time of assessment, maternal intelligence score, marital status (married/not married), education level (university/secondary school/up to primary), maternal smoking during pregnancy (yes/no) and breastfeeding (yes/no).
[a]We show the most relevant abilities measured. For all tests, direct scores were used in the analysis.
[b]A higher score indicates better cognitive function.
[c]A higher score indicates worse cognitive function.
[d]Immediate Recall Trial 5 (TAVECI).
* $p \leq 0.05$; † $p \leq 0.1$.

Table 6
Risk of being below or above the 20th or 80th percentile of cognitive function scores by log_e BPA Cr-standardized (μg/g) concentrations among 269 boys from the INMA-Granada cohort.

Cognitive functions[a]		BPA/Creatinine (μg/g) (log_e transformed, adjusted for covariatesd)		BPA/Creatinine (μg/g) (log_e transformed, adjusted for covariatesd[d])	
	n	OR	95% CI	OR	95% CI
Intelligence quotient (IQ)[b]	269	0.92	0.67;1.26	0.97	0.69;1.38
Verbal comprehension[b]	269	0.88	0.64;1.21	0.91	0.63;1.31
Attention					
Correct detections[b]	258	1.20	0.86;1.68	1.16	0.80;1.69
Impulsivity[c]	258	1.03	0.76;1.39	1.06	0.76;1.47
Omission errors[c]	258	1.13	0.83;1.54	1.10	0.78;1.56
Attention Index[b]	258	1.17	0.87;1.56	1.20	0.88;1.65
Verbal memory					
Immediate recall[b]	269	1.11	0.80;1.55	1.32	0.91;1.91
Short-term recall[b]	269	0.76	0.53;1.07	0.88	0.61;1.28
Long-term recall[b]	269	1.09	0.79;1.50	1.20	0.85;1.68
Visual-motor coordination[c]	268	–	–	–	–
Processing speed[b]	268	0.87	0.63;1.21	0.83	0.56;1.21
Executive Function					
Working Memory[b]	269	1.44	1.00;2.08*	1.51	1.01;2.25*
Verbal Fluency[b]	267	1.26	0.90;1.75	1.17	0.81;1.70
Impulsivity/Inhibition					
STROOP words[b]	267	0.99	0.71;1.40	1.05	0.72;1.53
STROOP colors[b]	267	0.76	0.55;1.06	0.85	0.60;1.22
STROOP words and colors[b]	267	0.96	0.69;1.35	1.05	0.73;1.52
Inhibitory Control (Interference)[b]	267	0.99	0.72;1.36	0.96	0.67;1.37
Hit rate[b]	255	0.83	0.57;1.24	0.82	0.53;1.28
False-alarm rate[c]	255	0.77	0.56;1.07	0.71	0.49;1.02
Shifting (s)[c]	268	0.87	0.64;1.18	0.83	0.60;1.16
Abstract reasoning[b]	269	1.18	0.84;1.65	1.11	0.76;1.62

OR: Odds Ratio; CI: confidence interval; s = seconds. * $p \leq 0.05$; † $p \leq 0.1$.

[a] We show the most relevant abilities measured. For all tests, scores were dichotomized into percentile 20 when a lower score meant worse cognitive function or percentile 80 when higher scoring meant worse cognitive function, except for attention index which was dichotomized into 0–1.

[b] A higher score indicates better cognitive function. Therefore, a higher OR means a higher risk of being below the 20th percentile.

[c] A higher score indicates worse cognitive function. Therefore, a higher OR means a higher risk of being above the 80th percentile.

[d] Models were adjusted for child's age (years), BMI (kg/m^2), smoking exposure at home (yes/no), mother's age at time of assessment (years), mother's intelligence score, marital status (married/unmarried), maternal education (university/secondary school/up to primary), smoking exposure during pregnancy (yes/no) and breastfeeding (yes/no).

(Findlay and Kohen, 2015), 1.3 ng/mL; and the DEMOCOPHES study on Spanish children at similar age (6–11 y) (Covaci et al., 2015), 1.83 ng/mL; among others (Hong et al., 2013). Urinary BPA concentrations can be influenced by the type and timing of sample collection (non-fasting between 17:00 and 20:00 h in the present study), country-specific BPA regulations, and differences in food intake and lifestyle.

Although no consistent associations with cognitive functions were observed in this study, with the exception of working memory, the relative effect sizes observed (changes of 1–2 points in the neuropsychological scales) are in the subclinical range. However, given that human BPA exposure is ubiquitous, adverse effects could occur at a population level (Bellinger, 2004). Importantly, a large number of people exposed to a small risk may generate many more cases of disease than a small number exposed to a high risk (Rose, 1985).

Our study has some limitations. First, the use of a single spot urine sample to characterize BPA exposure may increase the risk of exposure misclassification. However, this would probably lead to an underestimation rather than overestimation of BPA effects due to the non-persistent nature and short-term variability of this chemical (Betts, 2013). Second, the cross-sectional design of the study does not allow the inference of causal relationships. Third, no assessment was made of possible effects of co-exposure to other chemical compounds, such as phthalates and organohalogenated compounds, among others. Fourth, since multiple comparisons were performed, we cannot rule out that some of the few observed associations may be due to chance. However, this possibility is counteracted by our interpretation of results, which was based on the model robustness (comparison between unadjusted and adjusted models and between volume-based and creatinine-adjusted BPA concentrations), and on the comparison of associations observed in the current study with the available epidemiologic literature (Supplemental Table 1). Finally, sex-dependent relationships cannot be ruled out, because the study only included boys. The main study strengths include its contribution to the scant data available on BPA exposure and cognitive functions and the application by a trained psychologist of a comprehensive battery of tests. In addition, the analyses controlled for a large number of relevant covariates based on data from multiple questionnaires, physical examinations, and laboratory analyses of samples collected at the follow-up.

5. Conclusion

Results obtained in boys aged 9–11 years from the Spanish INMA-Granada cohort do not support an association between urinary BPA concentrations and cognitive abilities of the children, except for poorer working memory. Given our previous finding of a positive association between BPA and behavior problems in the same study population, these data suggest that BPA may be predominantly associated with their behavior.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2019.06.006.

References

Alonso-Magdalena, P., Ropero, A.B., Soriano, S., García-Arévalo, M., Ripoll, C., Fuentes, E., Quesada, I., Nadal, Á., 2012. Bisphenol-A acts as a potent estrogen via non-classical estrogen triggered pathways. Mol. Cell. Endocrinol. 355, 201–207. https://doi.org/10.1016/j.mce.2011.12.012.

Arambula, S.E., Belcher, S.M., Planchart, A., Turner, S.D., Patisaul, H.B., 2016. Impact of low dose oral exposure to bisphenol A (BPA) on the neonatal rat hypothalamic and hippocampal transcriptome: a CLARITY-BPA consortium study. Endocrinology 157,

3856–3872. https://doi.org/10.1210/en.2016-1339.
Arambula, S.E., Fuchs, J., Cao, J., Patisaul, H.B., 2017. Effects of perinatal bisphenol A exposure on the volume of sexually-dimorphic nuclei of juvenile rats: a CLARITY-BPA consortium study. Neurotoxicology 63, 33–42. https://doi.org/10.1016/j.neuro.2017.09.002.
Arambula, S.E., Jima, D., Patisaul, H.B., 2018. Prenatal bisphenol A (BPA) exposure alters the transcriptome of the neonate rat amygdala in a sex-specific manner: a CLARITY-BPA consortium study. Neurotoxicology 65, 207–220. https://doi.org/10.1016/j.neuro.2017.10.005.
Becker, K., Göen, T., Seiwert, M., Conrad, A., Pick-Fuß, H., Müller, J., Wittassek, M., Schulz, C., Kolossa-Gehring, M., 2009. GerES IV: phthalate metabolites and bisphenol A in urine of German children. Int. J. Hyg. Environ. Health 212, 685–692. https://doi.org/10.1016/j.ijheh.2009.08.002.
Bellinger, D.C.D.C., 2004. What is an adverse effect? A possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. Environ. Res. 95, 394–405. https://doi.org/10.1016/j.envres.2003.07.013.
Benedet, M.J., Alejandre, M.A., Pamos, A., 2001. In TAVECI, Test De Aprendizaje Verbal Infantil España-complutense. TEA Edicion. ed., Madrid, Spain.
Benton, A.L., Hamsher, K., 1989. In Multilingual Aplasia Examination, 2a Ed. Iowa City: The University of Iowa, 1989, 2nd ed. The University of Iowa, Department of Neurology and Psychology.
Betts, K.S., 2013. Unclear relationship: prenatal but not concurrent bisphenol A exposure linked to lower weight and less fat. Environ. Health Perspect. https://doi.org/10.1289/ehp.121-a135.
Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N., Lanphear, B.P., 2011. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics 128, 873–882. https://doi.org/10.1542/peds.2011-1335.
Braun, J.M., Muckle, G., Arbuckle, T., Bouchard, M.F., Fraser, W.D., Ouellet, E., Séguin, J.R., Oulhote, Y., Webster, G.M., Lanphear, B.P., 2017a. Associations of prenatal urinary bisphenol A concentrations with child behaviors and cognitive abilities 1–9. Environ. Health Perspect. 125, 067008. https://doi.org/10.1289/EHP984.
Braun, J.M., Yolton, K., Stacy, S.L., Erar, B., Papandonatos, G.D., Bellinger, D.C., Lanphear, B.P., Chen, A., 2017b. Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior. Neurotoxicology 62, 192–199. https://doi.org/10.1016/j.neuro.2017.07.027.
Braun, J.M., Bellinger, D.C., Hauser, R., Wright, R.O., Chen, A., Calafat, A.M., Yolton, K., Lanphear, B.P., 2017c. Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities. Neurotoxicology 58, 75–83. https://doi.org/10.1016/j.neuro.2016.11.009.
Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., Needham, L.L., 2008. Exposure of the U.S. Population to Bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ. Health Perspect. 116, 39–44. https://doi.org/10.1289/ehp.10753.
Cao, J., Rebuli, M.E., Rogers, J., Todd, K.L., Leyrer, S.M., Ferguson, S.A., Patisaul, H.B., 2013. Prenatal bisphenol A exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala. Toxicol. Sci. 133, 157–173. https://doi.org/10.1093/toxsci/kft035.
Casals-Casas, C., Desvergne, B., 2011. Endocrine Disruptors: from endocrine to metabolic disruption. Annu. Rev. Physiol. 73, 135–162. https://doi.org/10.1146/annurev-physiol-012110-142200.
Casas, L., Fernández, M.F., Llop, S., Guxens, M., Ballester, F., Olea, N., Irurzun, M.B., Rodríguez, L.S.M., Riaño, I., Tardón, A., Vrijheid, M., Calafat, A.M., Sunyer, J., Project, I.N.M.A., 2011. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37, 858–866. https://doi.org/10.1016/j.envint.2011.02.012.
Casas, M., Forns, J., Martinez, D., Avella-Garcia, C., Valvi, D., Ballesteros-Gomez, A., Luque, N., Rubio, S., Julvez, J., Sunyer, J., Vrijheid, M., 2015. Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. Environ. Res. 142, 671–679. https://doi.org/10.1016/j.envres.2015.07.024.
Conners, C., 1995. In Conners' Continuous Performance Test Computer Program: User's Manual.
Covaci, A., Den Hond, E., Geens, T., Govarts, E., Koppen, G., Frederiksen, H., Knudsen, L.E., Morck, T.A., Gutleb, A.C., Guignard, C., Cocco, E., Horvat, M., Heath, E., Kosjek, T., Mazej, D., Tratnik, J.S., Castano, A., Esteban, M., Cutanda, F., Ramos, J.J., Berglund, M., Larsson, K., Jonsson, B.A.G., Biot, P., Casteleyn, L., Joas, R., Joas, A., Bloemen, L., Sepai, O., Exley, K., Schoeters, G., Angerer, J., Kolossa-Gehring, M., Fiddicke, U., Aerts, D., Koch, H.M., 2015. Urinary BPA measurements in children and mothers from six European member states: overall results and determinants of exposure. Environ. Res. 141, 77–85. https://doi.org/10.1016/j.envres.2014.08.008.
Dessì-Fulgheri, F., Porrini, S., Farabollini, F., 2002. Effects of perinatal exposure to bisphenol A on play behavior of female and male juvenile rats. Environ. Health Perspect. 110 (Suppl 3), 403–407.
Diamond, A., 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750.
Donders, F.C., 1969. On the speed of mental processes. Acta Psychol. (Amst). 30, 412–431. https://doi.org/10.1016/0001-6918(69)90065-1.
Ehrlich, S., Calafat, A.M., Humblet, O., Smith, T., Hauser, R., 2014. Handling of thermal receipts as a source of exposure to bisphenol A. JAMA 311, 859–860. https://doi.org/10.1001/jama.2013.283735.
Ejaredar, M., Lee, Y., Roberts, D.J., Sauve, R., Dewey, D., 2017. Bisphenol A exposure and children's behavior: a systematic review. J. Expo. Sci. Environ. Epidemiol. 27, 175–183. https://doi.org/10.1038/jes.2016.8.
Fernández, M.F., Artacho-Cordón, F., Freire, C., Pérez-Lobato, R., Calvente, I., Ramos, R., Castilla, A.M., Ocón, O., Dávila, C., Arrebola, J.P., Olea, N., 2015. Trends in children's exposure to second-hand smoke in the INMA-Granada cohort: an evaluation of the Spanish anti-smoking law. Environ. Res. 138, 461–468. https://doi.org/10.1016/j.envres.2015.03.002.
Fernandez, M.F., Olmos, B., Granada, A., López-Espinosa, M.J., Molina-Molina, J.-M., Fernandez, J.M., Cruz, M., Olea-Serrano, F., Olea, N., 2007. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case–control study. Environ. Health Perspect. 115, 8–14. https://doi.org/10.1289/ehp.9351.
Findlay, L.C., Kohen, D.E., 2015. Bisphenol A and child and youth behaviour: canadian Health Measures Survey 2007 to 2011. Heal. reports 26, 3–9.
Freire, C., Molina-Molina, J.-M., Iribarne-Durán, L.M., Jiménez-Díaz, I., Vela-Soria, F., Mustieles, V., Arrebola, J.P., Fernández, M.F., Artacho-Cordón, F., Olea, N., 2019. Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities. Environ. Int. 127, 592–600. https://doi.org/10.1016/j.envint.2019.04.013.
Golden, C.J., 2005. In Stroop, Test de Colores y Palabras. 4a Ed, 4rd ed. TEA Ediciones, S.A., Madrid, Spain, pp. 2005 Madrid, Spain.
Gore, A.C., Krishnan, K., Reilly, M.P., 2018. Endocrine-disrupting chemicals: effects on neuroendocrine systems and the neurobiology of social behavior. Horm. Behav. https://doi.org/10.1016/j.yhbeh.2018.11.006.
Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., Sunyer, J., Project, I.N.M.A., 2012. Cohort profile: the INMA–INfancia y medio ambiente–(environment and childhood) project. Int. J. Epidemiol. 41, 930–940. https://doi.org/10.1093/ije/dyr054.
Hong, S.-B., Hong, Y.-C., Kim, J.-W., Park, E.-J., Shin, M.-S., Kim, B.-N., Yoo, H.-J., Cho, I.-H., Bhang, S.-Y., Cho, S.-C., 2013. Bisphenol A in relation to behavior and learning of school-age children. J. Child Psychol. Psychiatry 54, 890–899. https://doi.org/10.1111/jcpp.12050.
Jensen, T.K., Mustieles, V., Bleses, D., Frederiksen, H., Trecca, F., Schoeters, G., Andersen, H.R., Grandjean, P., Kyhl, H.B., Juul, A., Bilenberg, N., Andersson, A.-M., 2019. Prenatal bisphenol A exposure is associated with language development but not with ADHD-related behavior in toddlers from the Odense Child Cohort. Environ. Res. 170, 398–405. https://doi.org/10.1016/j.envres.2018.12.055.
Kaufman, A.S., Kaufman, N.L., 1997. In Kaufman Brief Intelligence Test (K.BIT) Manual. In: Cordero, A., Calonge, I. (Eds.), Spanish Adaptation. TEA Ediciones, S.A, Madrid, Spain, pp. 2000.
Komada, M., Itoh, S., Kawachi, K., Kagawa, N., Ikeda, Y., Nagao, T., 2014. Newborn mice exposed prenatally to bisphenol A show hyperactivity and defective neocortical development. Toxicology 323, 51–60. https://doi.org/10.1016/j.tox.2014.06.009.
Kundakovic, M., Gudsnuk, K., Franks, B., Madrid, J., Miller, R.L., Perera, F.P., Champagne, F.A., 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc. Natl. Acad. Sci. 110. https://doi.org/10.1073/pnas.1214056110.
Kuwahara, R., Kawaguchi, S., Kohara, Y., Cui, H., Yamashita, K., 2013. Perinatal exposure to low-dose bisphenol A impairs spatial learning and memory in male rats. J. Pharmacol. Sci. 123, 132–139.
Lakind, J.S., Naiman, D.Q., 2011. Daily intake of bisphenol A and potential sources of exposure: 2005-2006 National Health and Nutrition Examination Survey. . J. Expo. Sci. Environ. Epidemiol. 21, 272–279. https://doi.org/10.1038/jes.2010.9.
Lakind, J.S., Naiman, D.Q., 2015. Temporal trends in bisphenol A exposure in the United States from 2003-2012 and factors associated with BPA exposure: spot samples and urine dilution complicate data interpretation. Environ. Res. 142, 84–95. https://doi.org/10.1016/j.envres.2015.06.013.
Luo, G., Wang, S., Li, Z., Wei, R., Zhang, L., Liu, H., Wang, C., Niu, R., Wang, J., 2014. Maternal bisphenol a diet induces anxiety-like behavior in female juvenile with neuroimmune activation. Toxicol. Sci. 140, 364–373. https://doi.org/10.1093/toxsci/kfu085.
Maserejian, N.N., Shrader, P., Trachtenberg, F.L., Hauser, R., Bellinger, D.C., Tavares, M., 2014. Dental sealants and flowable composite restorations and psychosocial, neuropsychological, and physical development in children. Pediatr. Dent. 36, 68–75.
Maserejian, N.N., Trachtenberg, F.L., Hauser, R., McKinlay, S., Shrader, P., Bellinger, D.C., 2012a. Dental composite restorations and neuropsychological development in children: treatment level analysis from a randomized clinical trial. Neurotoxicology 33, 1291–1297. https://doi.org/10.1016/j.neuro.2012.08.001.
Maserejian, N.N., Trachtenberg, F.L., Hauser, R., McKinlay, S., Shrader, P., Tavares, M., Bellinger, D.C., 2012b. Dental composite restorations and psychosocial function in children. Pediatrics 130, e328–38. https://doi.org/10.1542/peds.2011-3374.
Mhaouty-Kodja, S., Belzunces, L.P., Canivenc, M.-C., Schroeder, H., Chevrier, C., Pasquier, E., 2018. Impairment of learning and memory performances induced by BPA: evidences from the literature of a MoA mediated through an ED. Mol. Cell. Endocrinol. https://doi.org/10.1016/j.mce.2018.03.017.
Michałowicz, J., 2014. Bisphenol A - Sources, toxicity and biotransformation. Environ. Toxicol. Pharmacol. 37, 738–758. https://doi.org/10.1016/j.etap.2014.02.003.
Molina-Molina, J.-M., Amaya, E., Grimaldi, M., Sáenz, J.-M., Real, M., Fernández, M.F., Balaguer, P., Olea, N., 2013. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol. Appl. Pharmacol. 272, 127–136. https://doi.org/10.1016/j.taap.2013.05.015.
Molina-Molina, J.M., Jiménez-Díaz, I., Fernández, M.F., Rodriguez-Carrillo, A., Peinado, F.M., Mustieles, V., Barouki, R., Piccoli, C., Olea, N., Freire, C., 2019. Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain. Environ. Res. 170, 406–415. https://doi.org/10.1016/j.envres.2018.12.046.
Mustieles, V., Ocón-Hernandez, O., Mínguez-Alarcón, L., Dávila-Arias, C., Pérez-Lobato, R., Calvente, I., Arrebola, J.P., Vela-Soria, F., Rubio, S., Hauser, R., Olea, N., Fernández, M.F., 2018a. Bisphenol A and reproductive hormones and cortisol in peripubertal boys: the INMA-Granada cohort. Sci. Total Environ. 618, 1046–1053.

https://doi.org/10.1016/j.scitotenv.2017.09.093.
Mustieles, V., Messerlian, C., Reina, I., Rodríguez-Carrillo, A., Olea, N., Fernández, M., 2018b. Is Bisphenol A (BPA) a threat to children's behavior? J Ment. Heal. Clin Psychol. 2, 6–9. https://doi.org/10.1016/S1474.
Mustieles, V., Pérez-Lobato, R., Olea, N., Fernández, M.F., 2015. Bisphenol A: human exposure and neurobehavior. Neurotoxicology 49, 174–184. https://doi.org/10.1016/j.neuro.2015.06.002.
Nakiwala, D., Peyre, H., Heude, B., Bernard, J.Y., Béranger, R., Slama, R., Philippat, C., Charles, M.A., De Agostini, M., Forhan, A., Heude, B., Ducimetière, P., Kaminski, M., Saurel-Cubizolles, M.J., Dargent-Molina, P., Fritel, X., Larroque, B., Lelong, N., Marchand, L., Nabet, C., Annesi-Maesano, I., Slama, R., Goua, V., Magnin, G., Hankard, R., Thiebaugeorges, O., Schweitzer, M., Foliguet, B., Job-Spira, N., Bernard, J., De Lauzon-Guillain, B., Germa, A., Pierre, F., Lepeule, J., Botton, J., 2018. In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. Environ. Heal. A Glob. Access Sci. Source 17, 1–11. https://doi.org/10.1186/s12940-018-0359-0.
Nesan, D., Sewell, L.C., Kurrasch, D.M., 2018. Opening the black box of endocrine disruption of brain development: lessons from the characterization of Bisphenol A. Horm. Behav. https://doi.org/10.1016/j.yhbeh.2017.12.001.
Patisaul, H.B., Bateman, H.L., 2008. Neonatal exposure to endocrine active compounds or an ERβ agonist increases adult anxiety and aggression in gonadally intact male rats. Horm. Behav. 53, 580–588. https://doi.org/10.1016/j.yhbeh.2008.01.008.
Patisaul, H.B., 2019. Achieving CLARITY on Bisphenol A (BPA), brain and behavior. J. Neuroendocrinol. e12730. https://doi.org/10.1111/jne.12730.
Perera, F., Vishnevetsky, J., Herbstman, J.B., Calafat, A.M., Xiong, W., 2012. Prenatal Bisphenol A exposure and child behavior in an Inner-City Cohort. Env. Heal. Perspect 1190, 1190–1194. https://doi.org/10.1289/ehp.1104492.
Perez-Lobato, R., Mustieles, V., Calvente, I., Jimenez-Diaz, I., Ramos, R., Caballero-Casero, N., Lopez-Jimenez, F.J., Rubio, S., Olea, N., Fernandez, M.F., 2016. Exposure to bisphenol A and behavior in school-age children. Neurotoxicology 53, 12–19. https://doi.org/10.1016/j.neuro.2015.12.001.
Perez-Lobato, R., Ramos, R., Arrebola, J.P., Calvente, I., Ocon-Hernandez, O., Davila-Arias, C., Perez-Garcia, M., Olea, N., Fernandez, M.F., 2015. Thyroid status and its association with cognitive functioning in healthy boys at 10 years of age. Eur. J. Endocrinol. 172, 129–139. https://doi.org/10.1530/eje-14-0093.
Philippat, C., Nakiwala, D., Calafat, A.M., Botton, J., De Agostini, M., Heude, B., Slama, R., 2017. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. Environ. Health Perspect. 125, 97014. https://doi.org/10.1289/EHP1314.
Poimenova, A., Markaki, E., Rahiotis, C., Kitraki, E., 2010. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. Neuroscience 167, 741–749. https://doi.org/10.1016/j.neuroscience.2010.02.051.
Porrini, S., Belloni, V., Della Seta, D., Farabollini, F., Giannelli, G., Dessì-Fulgheri, F., 2005. Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. Brain Res. Bull. 65, 261–266. https://doi.org/10.1016/j.brainresbull.2004.11.014.
Rebuli, M.E., Cao, J., Sluzas, E., Delclos, K.B., Camacho, L., Lewis, S.M., Vanlandingham, M.M., Patisaul, H.B., 2014. Investigation of the effects of subchronic low dose oral exposure to bisphenol A (BPA) and ethinyl estradiol (EE) on estrogen receptor expression in the juvenile and adult female rat hypothalamus. Toxicol. Sci. 140, 190–203. https://doi.org/10.1093/toxsci/kfu074.
Reitan, R.M., 1958. Validity of the trail making test as an indicator of organic brain damage. Percept. Mot. Skills 8, 271–276. https://doi.org/10.2466/pms.1958.8.3.271.
Roen, E.L., Wang, Y., Calafat, A.M., Wang, S., Margolis, A., Herbstman, J., Hoepner, L.A., Rauh, V., Perera, F.P., 2015. Bisphenol A exposure and behavioral problems among inner city children at 7-9 years of age. Environ. Res. 142, 739–745. https://doi.org/10.1016/j.envres.2015.01.014.
Rose, G., 1985. Sick individuals and sick populations. Int. J. Epidemiol. 14, 32–38. https://doi.org/10.1093/ije/14.1.32.
Rubin, B.S., Lenkowski, J.R., Schaeberle, C.M., Vandenberg, L.N., Ronsheim, P.M., Soto, A.M., 2006. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. Endocrinology 147, 3681–3691. https://doi.org/10.1210/en.2006-0189.
Stacy, S.L., Papandonatos, G.D., Calafat, A.M., Chen, A., Yolton, K., Lanphear, B.P., Braun, J.M., 2017. Early life bisphenol A exposure and neurobehavior at 8 years of age: identifying windows of heightened vulnerability. Environ. Int. 107, 258–265. https://doi.org/10.1016/j.envint.2017.07.021.
Tando, S., Itoh, K., Yaoi, T., Ikeda, J., Fujiwara, Y., Fushiki, S., 2007. Effects of pre- and neonatal exposure to bisphenol A on murine brain development. Brain Dev. 29, 352–356. https://doi.org/10.1016/j.braindev.2006.10.003.
Tando, S., Itoh, K., Yaoi, T., Ogi, H., Goto, S., Mori, M., Fushiki, S., 2014. Bisphenol A exposure disrupts the development of the locus coeruleus-noradrenergic system in mice. Neuropathology 34, 527–534. https://doi.org/10.1111/neup.12137.
Vandenberg, L.N., Chahoud, I., Heindel, J.J., Padmanabhan, V., Paumgartten, F.J.R., Schoenfelder, G., 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ. Health Perspect. 118, 1055–1070. https://doi.org/10.1289/ehp.0901716.
Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24, 139–177. https://doi.org/10.1016/j.reprotox.2007.07.010.
Wechsler, D., 2007. WISC-IV.Wechsler intelligence scale for children. Nueva York: The Psychological Corporation. (adaptación española): WISC-IV. Escala de Inteligencia Wechsler para niños. TEA Ediciones, S.A., Madrid, pp. 2007.
Weinberger, B., Vetrano, A.M., Archer, F.E., Marcella, S.W., Buckley, B., Wartenberg, D., Robson, M.G., Klim, J., Azhar, S., Cavin, S., Wang, L., Rich, D.Q., 2014. Effects of maternal exposure to phthalates and bisphenol A during pregnancy on gestational age. J. Matern. Fetal. Neonatal. Med. 27, 323–327. https://doi.org/10.3109/14767058.2013.815718.
Wetherill, Y.B., Akingbemi, B.T., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenschein, C., Watson, C.S., Zoeller, R.T., Belcher, S.M., 2007. In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol. 24, 178–198. https://doi.org/10.1016/j.reprotox.2007.05.010.
Wirt, T., Schreiber, A., Kesztyüs, D., Steinacker, J.M., 2015. Early Life Cognitive Abilities and Body Weight: cross-sectional study of the association of inhibitory control, cognitive flexibility, and sustained attention with BMI percentiles in primary school children. J. Obes. 2015, 1–10. https://doi.org/10.1155/2015/534651.
Xu, X., Hong, X., Xie, L., Li, T., Yang, Y., Zhang, Q., Zhang, G., Liu, X., 2012. Gestational and lactational exposure to bisphenol-A affects anxiety- and depression-like behaviors in mice. Horm. Behav. 62, 480–490.
Xu, X., Zhang, J., Wang, Y., Ye, Y., Luo, Q., 2010. Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-D-aspartate receptors of hippocampus in male offspring mice. Horm. Behav. 58, 326–333. https://doi.org/10.1016/j.yhbeh.2010.02.012.