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Is Bisphenol A (BPA) a Threat to Children's Behavior?

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ABSTRACT

In 2015 we reviewed the state of knowledge regarding the potential impact of bisphenol A (BPA) exposure on child neurobehavior. At that time, we expressed concern about the effects of BPA on children's behavior, especially when exposure takes place in utero. Since then, the number of human studies addressing the BPA-neurobehavior hypothesis has doubled, most of them reinforcing previous prenatal associations and frequently showing differences between boys and girls. An increasing number of studies have also shown an association between postnatal BPA exposure and diverse neurobehavioral impairments, including attention-deficit and hyperactivity disorder (ADHD). It may never be possible to establish a causal link between this specific endocrine disruptor and a particular neurobehavioral endpoint; however, research data on the relationship between human BPA exposure and children's behavior has revealed a relatively consistent pattern that cannot be ignored. The mounting experimental and epidemiologic evidence on neurobehavioral effects support more than ever the need to apply the precautionary principle during development, especially in relation to pregnant women and children. It seems that the time to act has arrived.

Neurobehavioral disabilities affect millions of children worldwide, and the prevalence of some neurodevelopmental disorders appears to be increasing. Subclinical symptoms are even more frequent and also contribute to a poorer quality of life and lower academic achievement[1]. Epidemiologic and animal studies have demonstrated that exposure to several families of endocrine-disrupting chemicals (EDCs) contribute to the risk of neurodevelopmental impairment[1,2].

Bisphenol A (BPA) is a well-known EDC that can interfere with hormonal balance, even at low doses, *via* multiple steroid hormone receptors that mediate a myriad of cellular effects[3]. The mechanistic understanding of its effects is particularly complex: BPA can bind not only to nuclear and membrane estrogen receptors but also to thyroid, glucocorticoid, and peroxisome proliferator-activated receptors, and it can also interact with steroidogenic enzymes, among other molecular targets[4,5]. This biological promiscuity might explain the pleiotropic effects exerted by BPA on behavior, reproduction, and metabolism[6,7]. The developing brain is a key target for this compound, and pre-, peri- and post-natal BPA exposure has been linked to a variety of altered behaviors, as demonstrated in multiple experimental models[3].

In 2015 we reviewed the state of knowledge on the relationship between human BPA exposure and neurobehavior[5]. We expressed

concern about the effects of BPA on children's behavior, especially when exposure takes place *in utero*. Although only 12 epidemiologic studies were available at that time, their findings pointed in the same direction as experimental studies, suggesting a negative impact of prenatal BPA exposure on children's neurobehavioral functioning in a sex-dependent manner[5]. The results suggested that male fetuses were more frequently affected by prenatal BPA exposure than females, in line with the current hypothesis of environmental intrauterine sex-dependent vulnerability[8].

Since March 2015, the number of human studies addressing the BPA-neurobehavior hypothesis has doubled[9–19], most of them reinforcing previous associations and frequently showing differences between boys and girls. For example, earlier findings by Perera et al. (2012)[20] and Roen et al. (2015)[21] were confirmed by Perera et al. (2016)[13], showing a consistent longitudinal pattern of internalizing problems, including anxiety and depression symptoms, among boys from childhood to adolescence in a birth cohort from the U.S.. More recently, Casas et al. (2015)[9] in Spain, Philippat et al. (2017)[15] in France, and Braun et al. (2017)[14] in Canada all supported the findings of previous studies by Harley et al. (2013)[22] in California and by Evans et al. (2014)[23] in a multicenter U.S. cohort. These reported more frequent behavior problems related to prenatal BPA exposure in the males than in the females. Notably, Braun and colleagues (2017)[14] studied 812 mother-child pairs belonging to the Maternal–Infant Research on Environmental Chemicals (MIREC) study, finding that higher prenatal urinary BPA concentrations were significantly associated with more frequent internalizing problems among three-year-old boys and with poorer executive function and higher social impairments. In contrast, two birth cohorts observed more behavior problems[24] and social impairments[17] related to prenatal BPA exposure in girls than in boys. Overall, epidemiologic data support a probable negative effect of prenatal BPA exposure on children's behavior in a sex-dependent manner.

An increasing number of studies show that postnatal BPA exposure is also associated with diverse neurobehavioral impairments among both boys and girls[10,11,16,21,22]. For example, some studies, including two representative national surveys, have reported associations with symptoms of attention-deficit and hyperactivity (ADHD) and with the prevalence of ADHD. Findlay and Kohen (2015)[10] observed positive cross-sectional associations between urinary BPA concentrations and ADHD symptoms in 2730 Canadian children/youths aged 6-17, while Tewar et al. (2016)[12] found a positive cross-sectional association between BPA concentrations and the risk of ADHD in 460 North American children/youths aged 8-15 years. A more recent case-control study in China also reported a stepwise increase in the risk of ADHD across increasing quartiles of urinary BPA concentrations[19]. These associations reinforce data from some previous prospective studies that found more ADHD symptoms in response to higher prenatal BPA concentrations[9,15,24]. These associations are also supported by experimental data[25,26].

The human brain is a sexually dimorphic organ, and major morphological differences are permanently shaped during prenatal development under the influence of steroid hormones, especially estrogen and aromatizable androgens[27,28]. BPA has been shown to alter sex-specific structural and behavioral patterns in experimental animals, including non-human primates, increasing, decreasing, and/or eliminating sex differences[29–32]. It is possible that BPA induces these effects through epigenetic modifications related to the estrogen-androgen balance, given evidence that BPA affects the gene expression of several estrogen receptor subtypes (ERα, ERβ and ERγ) in a sex- and brain region-specific manner[29]. Hence, *in utero* BPA exposure could predetermine later responses of certain brain areas to steroid hormones. Moreover, a recent high-quality experimental study by the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) demonstrated that low BPA doses *in utero* alter the rat brain transcriptome, mainly in the hypothalamus, finding sex-specific effects on hypothalamic ERα and ERβ expression[33].

More than 90% of Europeans and Americans have detectable concentrations of BPA in their urine, and diet is considered the main source of BPA exposure in humans[34–37]. Despite the ubiquity of BPA, its non-persistence and short biological half-life and the episodic nature of its exposure make BPA characterization very difficult, frequently producing an important degree of exposure misclassification. This results in a greater tendency to obtain null results, the so-called attenuation bias[15,38]. Therefore, it is possible that we have been systematically underestimating the effects of BPA, and researchers in the field should consider the potential impact of this attenuation when interpreting epidemiologic findings[11,15,38]. However, despite these methodological limitations, the overall picture of the relationship between human BPA exposure and behavior is relatively consistent across studies and populations. Moreover, the widespread nature of exposure to BPA means that even subtle changes in behavior at the individual level may have relevant effects at the population level, with public health repercussions[39,40].

In 2008, a National Toxicology Program assessment, based on animal data, reported that BPA-related neural and behavioral endpoints were a major concern for fetuses, infants, and children[41]. Since then, some governments have implemented preventive measures, such as the banning of BPA in baby bottles by Canada and subsequently by the European Union[42,43], and the total prohibition of BPA

in France[44]. Additionally, regulatory organizations such as the European Food Safety Authority (EFSA) have been progressively reducing their estimation of the tolerable daily intake (TDI) in subsequent risk assessments. Thus, the TDI for BPA was lowered from 50 μg/kg bw/day to 4 μg/kg bw/day in 2015[45]. Nevertheless, recent well-conducted experimental studies have shown that BPA can impact the brain and behavior of rats at doses near to or even below the current TDI[33,46], and it has been suggested that EFSA's temporary tolerable daily intake of 4μg/kg bw/day may not be "sufficiently protective" for humans in the general population[46]. EFSA's forthcoming assessment will be an opportunity to integrate new experimental and epidemiologic data and provide evidence in support of action to protect children's behavior.

BPA is commonly found in food packaging materials, being used in the manufacture of polycarbonate plastics and in the epoxy resin liners of food cans. The greater public awareness around BPA has been reflected by the increased popularity of "BPA-free" products[47]. However, many of these products are manufactured using bisphenol analogues, including bisphenol S and F (BPS and BPF), which have been shown to be at least as hormonally active as BPA[48]. Furthermore, experimental studies of bisphenol substitutes such as BPS and BPF suggest similar and in some cases greater adverse neurobehavioral effects than those associated with BPA[49].

It may never be possible to establish a causal link between a specific EDC and a particular neurobehavioral endpoint[50]. Nevertheless, it is impossible to ignore the consistent and accumulating human evidence on the effects of BPA on child neurobehavior. While future research will provide greater clarity, the mounting experimental and epidemiologic data on its neurobehavioral effects support more than ever the need to apply the precautionary principle during development, especially in relation to pregnant women and children[5,51]. It seems that the time to act has arrived[52].

Conflict of interest

The authors declare no actual or potential financial conflicts of interest.

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