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Does Bisphenol A contribute to autism spectrum disorder?

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ABSTRACT

Autism Spectrum Disorder (ASD) includes a range of conditions classified as neurodevelopmental disorders that have an onset from infancy. Multiple factors have been identified as causes for the autism spectrum disorder; however, the cascade of the disease is still not clearly defined. An increasing number of cases have been reported globally, for instance in US, UK, Canada and Australia. Environmental factors were suspected to be one of the causes. Bisphenol A (BPA) is an Endocrine Disruptor Compound (EDC) and used primarily as a monomer for the production of polycarbonate and epoxy resins, especially in feeding bottles for infants. Ongoing discussions are currently in progress on the reported low-dose effects of BPA, particularly its neurodevelopmental and behavioural effects. Many countries have banned the usage of BPA due to its harmful effects on children. This review aims at presenting an overview of the association between exposure to BPA and the neurobehavioural changes it triggers in children. Articles were obtained from the Science Direct and ProQuest search engines. The keywords used in the search were 'BPA' or 'bisphenol A' and 'autism'. Fourty-seven articles were shortlisted, of which only five that fulfilled the requisite criteria were selected for review. All of them were cohort studies. Overall, an association has been established between prenatal and childhood exposure to BPA and neurobehavioural changes. The exposure during pregnancy was observed to have a greater impact on children. Earlier exposure during the prenatal period resulted in stronger associations. However, no association was found between BPA concentration of the child and neurobehavioural outcomes.

KEYWORDS: autism spectrum disorder (ASD), bisphenol A (BPA), children, neurobehaviour

INTRODUCTION

Autism Spectrum Disorder (ASD) involves a range of conditions classified as neurodevelopmental disorders that have an onset from infancy. Its clinical presentation is characterised by impairment in the reciprocal social interaction and communication with others, and by a preference for repetitive, stereotyped behaviours. ASD is diagnosed according to the guidelines listed in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition - Text Revision* (DSM-IV-TR). The manual currently defines five disorders, also termed Pervasive Developmental Disorders (PDDs), as ASD: Autistic Disorder (classic autism), Asperger's disorder (Asperger syndrome), Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), Rett's disorder (Rett syndrome) and Childhood Disintegrative Disorder (CDD) [1].

According to the most recent report by the Autism and Developmental Disabilities Monitoring (ADDM) Network (2008), the overall estimated prevalence of ASDs among the 14 ADDM sites in the US is 11.3 per 1,000 (one in 88). This shows an increasing trend compared with the earlier surveillance done in 2006 and 2002, which revealed a prevalence of 9.0 and 6.4 per 1,000 children, respectively. Therefore, there has been a 23% increment in prevalence compared to the data reported in 2006 [2].

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Autism is a neuropsychiatric disorder. Multiple factors have been identified as the cause for the Autism Spectrum Disorder, although the cascade of the disease is still not clearly defined [3]. One of the most frequently identified causes for this condition is the genetic factor as reported by Folstein and Rutter in 1977 in their twin study [4], and the gene region identified was 15q11-13 [5]. Recent studies have implied that Autism Spectrum Disorder is due to four major causes, namely immune dysregulation or inflammation, oxidative stress, environmental toxicant exposures and mitochondrial dysfunction [6].

Bisphenol A (BPA)

Bisphenol A (BPA) is an Endocrine Disruptor Compound (EDC) used primarily as a monomer for the production of polycarbonate and epoxy resins. BPA is one of the highest production-volume chemicals worldwide, and is also known as a plastic monomer. Current estimates indicate that more than 8 billion pounds of BPA are produced annually to meet consumer demand, and approximately 100 tons are released into the atmosphere each year as a result of the production [7].

In humans, orally administered BPA is well-absorbed and undergoes a complete first-pass metabolism in the liver to BPA-glucuronide as the major metabolite, which is rapidly excreted in the urine, with a half-life of less than 6 hours. Bisphenol A-sulphate has been reported as a minor urinary metabolite of BPA in humans. As this first-pass metabolism is highly effective, there is an extremely low systemic availability of free BPA in humans after oral exposure. BPA-glucuronide and the minor urinary metabolite BPA-sulphate do not interfere with the hormonal regulation of reproduction. Therefore, these conjugation reactions represent the detoxification pathways [8].

However, in human neonates, some metabolic pathways, e.g. glucuronidation (2-5 fold lower in premature neonates) and some excretory functions, e.g. glomerular filtration (1.7 fold lower), have a lower efficiency compared with that of adults; these functions reach their full capacities only within one and seven months after birth, respectively [8]. Therefore, infants and children are more susceptible to BPA exposure and the effect on their health is greater since their detoxifying mechanism is still immature. From the data on the Expert Meeting of WHO [9], the mean exposure of exclusively breastfed babies (0 to 6 months) to BPA is estimated to be 0.3 μg/kg body weight per day, and exposure at the 95th percentile is estimated to be 1.3 μg/kg body weight per day. However, the exposure to BPA decreased relative to body weight. There are also many studies relating to the exposure of the foetuses resulting from the mother's consumption during the perinatal period [8].

A study done by Mustafa Ali in the general population of seven Asian countries, namely China, India, Japan, Korea, Kuwait, Malaysia and Vietnam, revealed that BPA was detected in 94.3% of the samples analysed, with concentrations ranging from < 0.1 to 30.1 ng/mL. The geometric mean concentration of BPA for the entire sample set from seven countries was 1.20 ng/mL. The highest median concentration of BPA was found in the urine samples from the age group of less than 19 years [10].

Exposure to BPA has been connected with negative health effects. Concern regarding the effects of BPA is greatest for infants and young children due to their immature systems for detoxifying chemicals. Many animal and human studies were conducted, relating BPA with neurobehavioural changes [11, 12, 13, 14, 15]. Discussions are ongoing regarding the effects of BPA, in particular, the neurodevelopmental and behavioural effects in laboratory animals and on the immaturity of the foetal and neonatal metabolic pathways.

On considering the effects, a ban on import, manufacture, advertisement and sale of feeding bottles containing the organic compound Bisphenol A or BPA was implemented in many countries including Malaysia. The ban was in line with Regulation 27A (1) of the Food Regulations 1985 [16]. This review aims at presenting an overview of the association between the exposure to BPA and the neurobehavioural changes in children.

METHODOLOGY

Articles were obtained from the Science Direct and ProQuest search engines. The keywords used in the search were 'BPA' or 'bisphenol A' and 'autism'. The use of other search terms such as 'Autism Spectrum Disorder' and 'neurobehavioural' did provide additional papers. From the Science Direct search engine, a total of 2,225 articles were found while

from ProQuest, another 140 articles were listed. Overlapping of articles was noted in both search engines. After screening the title, articles appropriate for the review were selected and a final total of 47 articles were extracted. The abstracts were subsequently reviewed to identify their aptness for the review. From the final total of articles, only five were ultimately selected for the review, excluding animal studies.

RESULTS

From a total of 47 articles, only five articles fulfilled the criteria for review. All of them were cohort studies. This was because the studies associated the outcome of child behaviour with BPA exposure during the antenatal periods. A summary of the five studies is given in Table 1.

DISCUSSION

Two of the five studies [17, 18] were from the same population, from the Health Outcomes and Measures of the Environment Study, Cincinnati, Ohio (USA). Published by the same author, it was an extension of his earlier study, involving additional assessments for behaviour via different sets of validated questionnaires (BRIEF-P). The other three studies were derived from the Health Outcomes and Measures of the Environment (HOME) Study cohort, The Mount Sinai Children's Environmental Health Study cohort and Center for the Health Assessment of Mothers and Children of Salinas study cohort.

The duration of the studies varied, depending on the time at which the neurobehaviour of the children had been assessed. The earliest assessment was done by Yolton *et al.* [19] which was approximately at five weeks after delivery. Others were done when the children were 2 years old, 3 years old, between 4 to 9 years old and the latest at 9 years of age as summarized in Table 1 [17, 18, 20, 21]. From this review, we can assess the time duration between the time of exposure and the time when the neurobehavioural symptoms started to become evident.

The questionnaires used were also different in all the studies. All the questionnaires were already validated and could assess different aspects of the neurobehavioural signs. Social Responsiveness Scale (SRS) is a rating scale of social behaviour characteristics of the autism spectrum and related disorders. This scale was used in the study by Miodovnik *et al.* [20]. This scale was further divided into subscales that included Social Awareness, Social Cognition, Social Communication, Social Motivation and Autistic Mannerisms. The Social Communication subdomain captures the deficits in pragmatic and expressive communication, which are the primary deficits seen in high-functioning children with ASDs. The cumulative deficits in these subdomains may reflect a higher level of socialisation difficulties and impairments in engaging in as well as interpreting fast-paced social interactions. By contrast, the more classically autistic behaviours captured by the Social Motivation (e.g. avoiding social interactions) and Autistic Mannerisms (e.g. highly restricted interests, stereotypical motor activity) subdomains reflect the more severe ASD symptoms. However, they are not diagnostic tools for ASD. Braun *et al.* [17, 18] and Harley *et al.* [21] used Behaviour Assessment System for Children 2 (BASC-2) in their studies. The BASC-2 is a parent-report assessment regarding the problem behaviour of the child in the community and home settings. The subscales analysed include aggression, attention, hyperactivity, depression, anxiety and somatisation.

The Behaviour Rating Inventory of Executive Function-Preschool (BRIEF-P) was used by Braun *et al.* [18] in which the analyses focused on five clinical scales, viz.:

(i) emotional control scores assess the ability to modulate emotions
(ii) inhibit scores reflect the capacity to control behavioural responses
(iii) plan/organise scores assess the ability to anticipate and to plan for future events, set goals and grasp the main idea
(iv) shift scores measure the capacity to transition to and from events, and
(v) working memory scores measure the ability to retain information in the mind for completing a task

NICU Network Neurobehavioural Scale (NNNS) was used by Yolton *et al.* [19] to assess neurobehaviour in early infancy. The NNNS is a comprehensive neurobehavioural assessment that evaluates neurological functioning, provides a behavioural profile and measures signs of stress in young infants. It is appropriate for infants at 30 to 40 weeks of gestational age.

Table 1. Summary of five cohort studies.

No	Reference	Study design	Sample population	Comparison	Exposure assessment	Other risk factors included	Results	Limitations & Strengths
1.	Braun *et al.* [17]	Cohort	Mothers and their children enrolled in Health Outcomes and Measures of the Environment Study, Cincinnati, Ohio	Early prenatal BPA exposure and BASC-2 scores at 2 years	Mothers provided three spot urine samples collected at: • 16 weeks of gestation • 26 weeks of gestation • at birth Children's spot urine samples at: • 1 year old • 2 years old • 3 years old	Maternal and child demographic factors • maternal age • race • education • marital status • annual household income • child sex Maternal depression during pregnancy	Log_{10}-transformed mean prenatal BPA concentrations were associated with externalizing scores, but only among females BPA concentrations collected around 16 weeks were more strongly associated with externalizing scores among all children, and this association was stronger in females than in males	**Limitations:** Children in the sample were 2 years of age at the time of behavioural assessment. Unmeasured confounding factors may be responsible for some or all of our observed associations Maternal BPA measurements taken at 26 weeks and at birth may be influenced by the glucose tolerance test and birthing process, respectively **Strengths:** Three urinary BPA measurements in the latter two-thirds of pregnancy to estimate gestational exposure. Used a valid and reliable measure of adaptive and problem behaviours in children
2.	Braun *et al.* [18]	Cohort	Mothers and their children enrolled in Health Outcomes and Measures of the Environment Study, Cincinnati, Ohio	Early prenatal BPA exposure, child BPA exposure and BASC-2 & BRIEF-P scores at 3 years old	Mothers provided three spot urine samples collected at: • 16 weeks of gestation • 26 weeks of gestation • at birth	Maternal and child demographic factors • maternal age • race • education • marital status • annual household income • child sex Maternal depression during pregnancy	10-fold increase in gestational BPA concentrations was associated with more anxious and depressed behaviour on the BASC-2 and poorer emotional control and inhibition on the BRIEF-P	**Limitations:** Sample size was modest, which reduced statistical power to test for gender modification Examined too many exposure-outcome associations, which increased the likelihood that results might include the null value by chance

Table 1 continued..

					Children's spot urine samples at: • 1 year old • 2 years old • 3 years old		The magnitude of the gestational BPA associations differed according to child gender; BASC-2 and BRIEF-P scores increased ranging from 9 to 12 points among girls, but changes were null or negative among boys	**Strength:** 6 spot urine samples from mothers and their children and averaged 2 urinary BPA concentrations during gestation or childhood, to reduce exposure variability
3.	Yolton *et al.* [19]	Cohort	Mother and infant pairs who were enrolled in the Health Outcomes and Measures of the Environment (HOME) Study	Early prenatal BPA exposure and early infant neurobehaviour (NNNS) at five weeks after delivery	Mother's urine BPA was collected from women at: • 16 weeks • 26 weeks	-maternal race -household income -marital status -maternal depression, -maternal BMI at 13-19 weeks -maternal blood lead level during pregnancy -alcohol use during pregnancy -marijuana use during pregnancy -maternal serum cotinine during pregnancy -infant weight change per month from birth to five weeks -infants who could potentially be at high risk for neurobehavioral deficits	There was no evidence of an association between prenatal BPA exposure and infant neurobehaviour	The date of mother's last menstrual period was used to estimate gestational age and can be an inexact measurement tool in determining the point of gestation

Table 1 continued..

4.	Miodovnik *et al.* [20]	Cohort	The Mount Sinai Children's Environmental Health Study	Maternal spot urine BPA samples and their child SRS score (between 4 and 9 years of age and between 7 and 9 years of age).	Maternal spot urine for BPA samples between 25 and 40 weeks gestation	-maternal age -maternal IQ -marital status at the time of follow-up -maternal education -child race -sex -child IQ -age at examination -urinary creatinine	No significant association of Social Responsiveness Scale score with BPA was found	**Limitation:** Parental reporting bias Did not rely on the clinical diagnosis of ASD but only on symptoms common to the disorders
5.	Harley *et al.* [21]	Cohort	Mothers and children enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	Between maternal urine BPA and child's urine BPA at 5 years of age with child behaviour at age 7 years and 9 years	Maternal urine BPA and children at 5 years of age	-maternal age -race/ethnicity -education level -marital status -country of birth -years of residence in the United States -smoking during pregnancy -maternal urinary concentrations of dialkyl phosphate (DAP) -number of siblings -family income -maternal depression -level of stimulation at home	Prenatal urinary BPA concentrations were associated with increased internalizing problems in boys, including anxiety and depression at 7 years old No associations were seen with prenatal BPA concentrations and behaviours in girls. Childhood urinary BPA concentrations were associated with increased externalizing behaviours, including conduct problems, in girls at age 7 and increased internalizing behaviours and inattention and hyperactivity behaviours in boys and girls at age 7	**Limitations:** BPA was measured in two urine samples collected during pregnancy and urine samples collected at age 5. May not represent on-going BPA exposure **Strength:** The use of biomarkers to assess early life BPA exposure Behaviour assessed by multiple observers

Different sets of questionnaires were used to assess the outcome of the child which raised the difficulty of comparing the results between the studies. If ASD was the main concern, then SRS might be the appropriate tool to be used. However, it is not applicable for use in early childhood assessment, for example in neonates.

There are two studies that measured the urine BPA level in children (done at 1, 2 and 3 years of age by Braun *et al.* [18] and at 5 years of age by Harley *et al.* [21]). The urine BPA level was assessed at different times of pregnancy in all the studies. In two of the studies, the childhood BPA level was assessed at 5 years of age [21] and at 3 years of age [18]. Most of the studies were interested in the outcome from gestational exposure rather than from recent exposure. Experimental studies with animals also indicated that gestational BPA exposure disrupted normal neurodevelopment, affecting sexually dimorphic behaviours such as aggression, anxiety, exploration and spatial memory [22, 23].

The confounder variables were adequately addressed in all the studies, in terms of choosing the associating variables and via data analysis. Mother and child surrounding factors were also considered during the selection of the covariates.

The results from three studies which used the same scale (BASC-2) showed positive associations between BPA exposure and neurobehavioural changes. Braun *et al.* [17] revealed that $\log_{10}$-transformed mean prenatal BPA concentrations were associated with the externalising scores, but only among females [$\beta = 6.0$; 95% confidence interval (CI), 0.1–12.0]. However, in the study performed in 2011, the analysis was done in greater detail, in which the gestational BPA concentrations were positively associated with BASC-2 anxiety, hyperactivity and depression scale, with the association being greater in girls. However, in the study by Harley *et al.* [21] the results showed no association between the prenatal BPA concentrations and any behaviour in girls. In boys, the higher maternal urinary BPA concentrations during pregnancy were associated with increased internalising problems at 7 years of age. The study reported increased symptoms of depression and anxiety in boys with higher prenatal BPA concentrations. No association was observed between childhood BPA concentrations and neurobehaviour, in the study by Braun *et al.* [18] although an association between childhood BPA concentrations and increased internalising scores were seen in 5-year-old children [21]. The development of sex-specific behaviour is mediated largely by the sex hormones in the foetal brain. Exposure to endocrine-disrupting compounds such as BPA during the earliest stages of development can impact behaviour, including aggression and anxiety in both males and females [24].

Exposure during pregnancy was noted to have a greater impact on the child. Braun *et al.* [17] in their study found that the BPA concentrations collected around 16 weeks of gestation were more strongly associated with the externalising scores among all the children compared with the concentration at 26 weeks and at birth. The other two studies, by Miodovnik *et al.* [20] and Yolton *et al.* [19] found no association at all between prenatal BPA exposure and the child responsiveness scale score. The early assessment age could have been the reason for the absence of association because neurobehaviour can be accurately measured after a particular time period in children.

CONCLUSION

Overall, an association was established between prenatal and childhood exposure to BPA and neurobehavioural changes. The influence of gender varied among the studies. The earlier exposure during the prenatal period resulted in stronger associations. Thus, preventive measures during the prenatal period definitely need to be considered. More studies are warranted using standardised tools to enable the results to be comparable.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ABBREVIATIONS

ADDM	:	Autism and Developmental Disabilities Monitoring
ASD	:	Autism Spectrum Disorder
BASC-2	:	Behaviour Assessment System for Children 2
BRIEF-P	:	Behaviour Rating Inventory of Executive Function-Preschool
BPA	:	Bisphenol A
CDC	:	Communicable Disease Control
COD	:	Childhood Disintegrative Disorders

DSM-IV-TR	:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision
EDC	:	Endocrine Disruptor Compound
ESFA	:	European Food Safety Authority
HOME	:	Health Outcomes and Measures of the Environment
NNNS	:	NICU Network Neurobehavioural Scale
ODD	:	Oppositional Defiant Disorders
PC	:	Polycarbonate
PDD	:	Pervasive Developmental Disorder
PDD-NOS	:	Pervasive Developmental Disorder Not Otherwise Specified
WHO	:	World Health Organization

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