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The association of environmental toxicants and autism spectrum disorders in children☆

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ABSTRACT

Autism spectrum disorders (ASDs) is a set of complex neurodevelopment disorders that is prevalent in children and is increasing at a steady rate in recent years. However, the etiology of autism is still poorly understood. Humans are at higher risk of chemical exposure than in the past as a result of the increasing usage of chemicals in various fields, including food preservation, agriculture, industrial production, etc. A number of environmental agents have been suggested as contributing factors to ASD pathogenesis, which includes heavy metals (Hg and Pb), persistent organic pollutants (DDT, PBDEs and PCBs) and emerging chemicals of concern (phthalates and BPA). These three main categories of toxicants could be the cause of ASD in children. Recent research into the causes of ASD that have been linked to environment factors are reviewed in this paper. There are evidence supporting the etiological link between exposure to environmental toxicants and the development of ASD. Children exposed to these toxicants in the environment exhibit signature traits of ASD and have been reported with high body burdens of these chemicals and/or their metabolites, which may provide an explanation for the observed relation, yet comprehensive evidence in humans is limited, highlighting the need for further research.

1. Introduction

Autism spectrum disorders (ASDs) is a set of complicated disorders related to neurodevelopmental that affects normal functioning of the brain and may consequently lead to lifelong disabilities (Hallmayer et al., 2011). Autism is characterized by well-documented biochemical imbalances such as redox imbalance, oxidative stress, and associated mitochondrial dysfunction (Kaur et al., 2014). ASD is typically diagnosed during childhood since children and infants are high-risk population groups and are more susceptible to neurological disorders than adults (Liew et al., 2015). Furthermore, symptoms of ASD manifest during the first three years of life as social deficits, communication difficulties, and cognitive delays (Hallmayer et al., 2011). Autistic individuals exhibit repetitive and stereotyped behaviors as well as restricted interests (Nevison, 2014). People with Asperger syndrome (considered as high-functioning autism) do not exhibit significant delays or difficulties in language or cognitive development, but may have difficulties with social skills, sensory input and require rigid routines whereby their environment is predictable and familiar (Austism Speaks Inc, 2016).

The prevalence of ASD has increased dramatically in the US from 1 in 2500 children in the early 1970s to a currently reported rate of 1 in 68, as estimated by the Centers for Disease Control and Prevention Center (CDC) (2014). Similar increasing trends have also been recorded in Europe and Asia. For instance, the current estimate of prevalence in the UK has reached as high as 157 per 10,000, whereas the incidence rate was only 4.4 per 10,000 between 1966 and 1991 and 12.7 per 10,000 between 1992 and 2001 (Quaak et al., 2013). In comparison to Western countries, recent epidemiology studies have estimated ASD prevalence as 14.8 per 10,000 in Asia (Sun et al., 2013). In China and Hong Kong, for

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example, it is estimated that 10.3 and 5.49 in every 10,000 children are diagnosed with autism (Sun et al., 2013; Wong and Hui, 2008). In general, there is a paucity of data regarding the prevalence of ASD in China. According to statistical data compiled by CDC (2016) from various studies that were undertaken between the period from 1964 to 2014, an average of about 1–2% of the population in Asia (Japan, Hong Kong, Taiwan, South Korea), Europe, and North America has been diagnosed with autism. The incidence of autism in boys has also been found to be significantly higher than in girls (NINDS, 2016). The continuously rising prevalence of ASD appears to be more notable in recent decades worldwide. This has aroused a much wider public concern, and substantial research efforts have been undertaken to elucidate the reasons behind this observed shift in prevalence. Various factors have been proposed, including broader diagnostic criteria, improvement in case ascertainment and increased awareness and recognition of ASD (Sun et al., 2013). However, these factors could only partly account for 1/3 of the increase in autism prevalence; the remaining portion of the increase could be attributable to actual incidence of autism (Hertz-Picciotto et al., 2006). There may also be many different factors that could cause ASD in a child, such as genetic, biologic and environmental factors which act alone or together. Therefore, the challenging question remains unanswered of what causes ASD, highlighting that more in-depth research and understanding into the complex causes of autism are needed.

In general, scientists agree that genetics is one risk factor that can cause the development of ASD, however, epigenetics, transcriptomics, immune system disruption and environmental factors may also play a role. The complex interactions between genes and environmental factors may occur before, during, and after pregnancy. Exposure to environmental toxicants such as mercury, lead, bisphenol A, phthalates, and nutrition deficiency such as folic acid, vitamin D, or fatty acid may be associated with an increased risk of ASD. Other factors such as mature maternal or paternal age, preterm delivery, low birthweight, maternal infection, maternal exposure to environmental pollutants, obstetric complications, use of certain medications during pregnancy, and maternal diabetes or obesity are also factors (Lampi et al., 2012; Xu et al., 2014). In a study of infertility treatments, there were no evidence to link the treatment with the risk of ASD among singleton births, and the data for multiple births were found to be inconclusive in a study of 77,403 children born in 1995–1998 (Grether et al., 2013).

The major purpose of the present article is to review whether there is a possible association between some environmental toxicants (namely heavy metals, persistent organic pollutants, and emerging chemicals of concern) and ASD in children, with the support of different types of studies. The associations between the most representative chemicals in each of the above categories, including mercury (Hg), lead (Pb), dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), bisphenol A (BPA), and phthalates will be discussed.

1.1. Hereditary components related to causation of autism

It is widely accepted that a strong hereditary component is implicated in ASD (Buxbaum and Hof, 2011; Johnson et al., 2013). Approximately 30–40% of all neurodevelopment disorders are caused by genetic factors alone (Landrigan et al., 2012). Fragile X and Rett syndrome have been identified as genetic causes. The genetic causation is supported further by twin, family and linkage studies. A substantial number of candidate autism susceptible genes at multiple loci have been identified by linkage; association and cytogenetic studies, suggesting polygenic factors contribute etiologically to autism (Hertz-Picciotto et al., 2006). It has also been demonstrated that concordance rates among monozygotic twins and recurrence risk in siblings can reach up to 70–90% and 2–14%, respectively, whereas the concordance rates in dizygotic twins (0–10%) appear to be no higher and even lower than the rates among siblings (Hallmayer et al., 2011; Hertz-Picciotto et al., 2006; Mitchell et al., 2012). However, a comprehensive study of autistic twins born between 1987 and 2004 reported a 60% concordance rate in monozygotic twins and 27% concordance in dizygotic twins, indicating environmental components shared by twins are linked with autism (Hallmayer et al., 2011).

A study involving the genetic testing of chromosomal abnormalities in 218 children in the US diagnosed with ASD born from 1983 to 2009 found that approximately 80% had negative genetic test results (NGTRs). About 20% had positive genetic test results (PGTRs), of which ~7% were probable de novo mutations. Of the 80% with NGTRs, the subjects examined did not possess any identifiable genetic findings from high-resolution blood chromosome or blood-chromosome microarray testing (Geier et al., 2016). Therefore, environmental factors seems to play an increasing role in ASD etiology. The findings also suggest that sociability scores of the children with NGTRs significantly worsened with age which seems to further indicate that an environmental component is a contributing factor to the development of ASD. On the contrary, sociability scores did not worsen with age for children with overall PGTRs. The results of another study on a cohort of 933 subjects (aged 13 months to 22 years old) provide support of chromosomal microarray analysis as part of the initial diagnostic evaluations of patients with ASD (Shen et al., 2010).

1.2. Environmental factors related to causation of ASD

Despite the significance of genetic roles in pathogenesis of autism, explorations on the association between environmental factors and autism have increased recently. US National Research Council (2000) estimated that exposure to environmental toxicants contribute to 3% of neurodevelopment disabilities directly. Moreover, a growing body of studies have shown that the developing brain of the fetus is exquisitely vulnerable to environmental toxicants. Therefore, prenatal exposure (especially during the first trimester of pregnancy) have greatest impact on the brain ranging from subclinical dysfunction at low levels of exposure up to overt toxicity, leading to a spectrum of neurodevelopment disorders (Landrigan, 2010). Furthermore, various environmental contaminants such as heavy metals and POPs have been a long-term concern of autism advocate due to their toxic and endocrine-disruptive nature (De Cock et al., 2012; Ko et al., 2013; Nowack et al., 2015).

The etiological factors implicated in autism development still remain elusive and controversial, however, it is commonly agreed that causes of ASD are heterogeneous and are attributed to complicated interactions between genetic factors and environmental pollutants interacting synergistically or in parallel with each other (Quaak et al., 2013; Rossignol et al., 2014).

2. Environmental toxicants

2.1. Heavy metals and autism

Heavy metals are naturally occurring elements with a relatively high density (>5.0 g/cm^3) or high atomic weight (Fergusson, 1990). Exposure to highly toxic heavy metals such as Hg and Pb can cause damage to brain cells, which lead to neurological defects, development delays, socio-behavioral disabilities and intellectual impairment (Gorini et al., 2014). Exposure during infancy and early childhood will lead to lifelong neurobehavioral changes in children, due to their weaker immune system and poorer detoxifying ability

with respect to adults. Therefore, recent studies focused on investigating the potential contribution of heavy metals to ASD development in children.

2.1.1. Mercury (Hg)

Being a ubiquitous element in the environment, the potent neurotoxicity of Hg has been known for centuries (Gorini et al., 2014). Most of the Hg pollution comes from industrial waste, such as coal combustion, waste incineration and mining activities (Zhang and Wong, 2007). Due to its relatively low boiling point, Hg can be vaporized easily. When it falls from air into aquatic systems, Hg will be bioaccumulated and biomagnified in aquatic food chains. The inorganic form of Hg can be transformed into its highly toxic organic form, methylmercury (MeHg), by microbial methylation (Dórea, 2008). MeHg can be easily absorbed by fish living in contaminated water and could be continuously accumulated in their bodies.

Therefore, the main Hg exposure pathways for humans are through inhalation and fish consumption, especially large carnivorous fish such as tuna possess extremely high concentrations of MeHg (Zhang and Wong, 2007). The human brain is a major target as MeHg can pass across the blood-brain barrier and hence produce severe and long-term neurological damages especially to children during their neurodevelopment stages (Davidson et al., 2006). MeHg is transferred to fetus and infant from the mother via the placenta and breastfeeding, respectively, and stored eight times as high as the mother (Geier et al., 2010). The first documented acute mercury poisoning episode was reported in Japan as Minamata disease, whereby patients displayed symptoms such as mental retardation or cerebral palsy, which are indistinguishable from signature traits of autism (Kondo, 2000). Moreover, the relationship between dietary MeHg exposure and neonatal neurologic function was examined in a study of 182 infants from Faroe Islands where seafood contamination is significant (Steuerwald et al., 2000). High levels of MeHg were detected in samples of maternal serum, hair, milk, and umbilical cord blood, suggesting that increased Hg exposures in children were associated with increased maternal seafood intake.

In addition, neurologic optimality score of each infant at two weeks of age decreased by 2.0 with respect to a 10-fold increase of Hg concentration in cord-blood. Therefore, prenatal exposure to MeHg seems to adversely affect intellectual development in children whose mothers had a high consumption of seafood contaminants during pregnancy. A number of studies reported elevated Hg levels in hair, nail and urine of autistic children as compared to the control, indicating the biological plausibility of mercury as a risk factor in autism development (Blaurock-Busch et al., 2011; Fido and Al-Saad, 2005; Ko et al., 2013; Lakshmi Priya and Geetha, 2011). Kern et al. (2016) identified 91 studies (from 1999 to February 2016) that examined the potential association between mercury exposure and ASD, and of these studies, 74% suggested Hg as a risk factor for ASD.

Thimerosal, which contains sodium ethyl-mercury thiosalicylate, $C_9H_9HgNaO_2S$ (49.55% Hg by weight) has been the subject of many studies to determine whether there is a link between childhood exposure to thimerosal and ASD. Thimerosal has been used since the 1930s as a preservative to prevent the growth of microbes in vaccines for children (CDC, 2015a,b; Kern et al., 2013). Vaccines for tetanus, hepatitis B (HepB), Haemophilus influenza type b (Hib), and meningococcal meningitis A, C, Y, and W-135 vaccines were preserved with thimerosal (0.01%) (Kern et al., 2013). Since 2001, thimerosal has not been used in vaccines for children in the United States, except for some flu vaccines. Flu vaccines packaged in multi-dose vials contain thimerosal whereas most single-dose vials and pre-filled syringes do not contain the preservative (CDC, 2015a,b). CDC recommends that children aged 6 months and older receive an annual flu vaccination. CDC (2015a,b) have reported that thimerosal-related studies carried out by CDC or with CDC's involvement have indicated that thimerosal is not a toxin and an association between thimerosal in vaccines and autism has not been found.

There are studies that have suggested a causal relationship between childhood exposure to thimerosal and ASD. In a review paper, Kern et al. (2016) presents eight epidemiology studies that did not find thimerosal in vaccines to be a risk factor for ASD and twelve epidemiology studies that have found thimerosal in vaccines to be a significant risk factor for ASD. For example, a case-control study showed significantly increased associations between exposure to Hg from thimerosal in *Haemophilus influenzae* type b (Hib)-containing vaccines administered within the first 15 months of age in infants who were subsequently diagnosed with ASD, in comparison to controls (Geier et al., 2015).

Kern et al. (2013) provided insight on abnormal sulfation chemistry, limited thiol availability, and decreased glutathione (GSH) reserve capacity in children diagnosed with an ASD and how these could lead to compromised oxidation/reduction (redox) and detoxification capacity, rending children more susceptible to the toxic effects of mercury in thimerosal. Being an antioxidant, GSH can prevent damage to important cellular components caused by reactive oxygen species such as free radicals. It plays an important role in the detoxification of xenobiotics. Thimerosal is a thiol inhibitor. It has been noted that Hg exposure inhibited the development of the cerebral GSH antioxidant system during the early postnatal period thus contributing to oxidative damage. The reduction of intracellular GSH also increased the toxic effects of thimerosal (Stringari et al., 2008; Kern et al., 2013). Although an ASD diagnosis is defined by psychological criteria such as impairments in social interaction, communication and stereotyped behavior patterns, there are also physical symptoms such as headaches, respiratory and food allergies, infections, gastrointestinal problems, sleep problems and eating disorders (Kern et al., 2013). These physical symptoms can serve as metabolic biomarkers and predisposing factors that can be identified and linked with ASD.

Although there are studies that suggest thimerosal in vaccines is a risk factor for ASD, global immunization is important in safeguarding the health of children against illnesses.

2.1.2. Lead (Pb)

Lead exists naturally in the earth crust and major sources of lead pollution are from industrial emissions and burning of fossil fuels (WHO, 2016). Humans are primarily exposed to Pb through ingestion of contaminated food and water while children are subjected to inadvertent ingestion of Pb paint (ATSDR, 2007). It has been known for centuries that Pb exhibits neurotoxic effects on the human central nervous system (CNS), especially in children (Gorini et al., 2014). Early studies on children with increased blood Pb concentration from US between 1970s and 1980s revealed deficits in memory, cognition, and behavior suggesting the detrimental effects of Pb on CNS (Landrigan et al., 1975; Needleman, 1988). Exposure to deteriorated Pb-based paints, Pb contaminated soil and dust as well as drinking water systems can lead to Pb poisoning (Levin et al., 2008). Patients of Pb poisoning are typically asymptotic, thus they may go undetected (National Library of Medicine (2004)). The effects of Pb poisoning towards children are especially significant. Stomachache, vomiting, unusual pale skin, or brain damage related symptoms like seizures, papilledema are the most notable ones. Other symptoms include socio-behavioral disabilities, slurred speech, and mental retardation (Table 1).

Epidemiological studies reported that Pb exposure during

childhood is associated with cognitive and intelligence quotient (IQ) deficits as well as behavioral abnormalities (Eubig et al., 2010). For instance, Lanphear et al. (2005) investigated 1333 children at 5–7 years of age to evaluate the link between intelligence test scores and Pb exposure. The results showed a negative relationship between IQ scores and blood concentration of Pb. Specifically, an increase in geometric mean blood Pb concentration from 2.4 to 30 μg/dL was linked to a 6.9 IQ point decrement (Lanphear et al., 2005). Furthermore, a significant elevation in Pb concentrations in both hair and nail samples from children with ASD has been noted when compared to a healthy control group (Lakshmi Priya and Geetha, 2011). Another study by Fido and Al-Saad (2005) found that autistic children from Kuwait displayed a Pb body burden that was almost two times higher than that of neurotypical children. The exposure to Pb which is prevalent at primitive e-waste recycling sites can cause postnatal disorders such as autism (Leung et al., 2008; Xu et al., 2016).

Collectively, Hg and Pb poisoning and autism show similar symptoms with both neurological and behavioral disorders (Table 1), and in turn, autistic patients reveal higher body loadings of these heavy metals with respect to healthy controls, suggesting that exposure to these metals may increase the risk of ASD in children.

2.2. Persistent organic pollutants (POPs) and autism

Persistent Organic Pollutants are organic compounds that are highly persistent in the environment and resistant to chemical, biological, and photolytic degradation (Wong, 2013). Additionally, their inherent lipophilic property, high toxicity and semivolatile nature make them easily accumulate in human and other animal food chains; adversely affect development functions of living organisms; and become more ubiquitous in the environment even in the South Pole (Pizzorno, 2013). Dichlorodiphenyltrichloroethane (DDT) is one of the most oldest POPs, firstly synthesized in 1874, which imposes toxic effects on different aspects of different creatures. Exposure to PBDEs and PCBs are of particular concern for human brain development. PBDEs and PCBs are known to disrupt normal endocrine and neurotransmission functions that are also implicated in autistic brains. Therefore, a hypothesis that PBDEs and PCBs might also serve as autism risk factors has emerged (Winneke, 2011).

2.2.1. Dichlorodiphenyltrichloroethane (DDT)

DDT, an organochlorine pesticide was first synthesized in 1874, and has been used for the prevention and control of pests on agriculture crops and insect rectors with impressive performance. The application of DDT was no longer permitted in the U.S. since 1972, due to its persistence and carcinogenic nature to both humans and the environment (ATSDR, 2002). A study showed that DDT cannot be easily degraded and last a long time (potentially hundreds of years) in the environment. When absorbed by the living organisms in bottom or lower levels of the food chain, the concentration of DDT accumulates at a higher rate in the body of living organisms in the higher food chain levels (EXTOXNET, 1996). The major human exposure pathways of DDT are via intake of contaminated food, from mother to infants through placenta and breastfeeding (ATSDR, 2002). Animal toxicology studies and epidemiology evidence indicate endocrine disrupting effects of DDT as a xenoestrogen with respect to human exposure, which may cause adverse reproduction and developmental effects (NIEHS, 2007). Further research have revealed that DDT constitutes an important risk factor in the neurodevelopment of children that may link DDT to the causation of ASD.

Ribas-Fitó et al. (2006) examined the relationship between DDT exposure and neurodevelopment in children at 4 years of age. Results showed that children with cord blood DDT concentration of >0.20 ng/ml displayed lower points in both verbal and memory scales in comparison to those with concentration of <0.05 ng/ml. This finding suggested that in utero exposure to DDT was inversely linked with cognitive skills among preschoolers, even at background and low-levels of concentrations.

Shutoh et al. (2009) studied the effects of DDT (dosage: 0, 0.006, 0.06, 0.6, 6 and 60 mg/kg/day) on brain development of young male rats. Results showed that mRNA expression remained unchanged inside the hippocampus, but the expression patterns of 40 genes in the hypothalamus were altered between the two groups receiving 0.06 mg/kg/day and 0.6 mg/kg/day. DDT may also poison young human brains and cause physical or psychological effects, such as lack of focus, IQ deficiency, language ability lacking or missing, etc. While these problems are developing along with the growth of children, they may also lead to more serious symptoms such as social withdrawal, memory loss, and socio-behavioral disability (see Table 2).

2.2.2. Polychlorinated biphenyls (PCBs)

PCBs are synthetic organic compounds containing chlorine attached to biphenyl, which have been widely used for industrial applications. Although the use of PCBs has been banned in the early 1980s, its long persistence in environment media and limited biodegradability still put people at risk of exposure. Almost 90% of PCBs found in the human body occur from intake of dairy products and animal fat (Ross, 2004). PCBs are of concern as neurodevelopmental toxicants as they can bioaccumulate in lipid-rich tissues, disrupt endocrine and neurotransmitter systems as well as intracellular signaling pathways (Mitchell et al., 2012).

Table 1
Summary of the effects of Hg and Pb exposures on cognitive functioning in children and comparison of the similarities to ASD symptoms.

Heavy metals	Effects on children	Exposure Pathways	Target Organs	Similarity to ASDs symptoms	Reference
Mercury (Hg)	Social withdrawal	Inhalation and fish consumption	Amygdala	Very high	Gorini et al. (2014)
	Neurological and behavioral disorders		Central nervous system	Somehow similar	
	Lack of concentration		Frontal lobe	Very high	
	Rapid body temperature change		Frontal lobe/central nervous system	Not clear	
	Memory loss		Hippocampus	Somehow related	
Lead (Pb)	IQ deficits	Pb paint, contaminated food and water	Brain	Sometimes	Gorini et al. (2014)
	Socio-behavioral disabilities		Amygdala	High	
	Decreased attention		Frontal lobe	Very high	
	Intellectual impairment		Brain	Not clear	
	Slurred speech		Language center	High	

Table 2
Summary of the effects of POPs exposure on cognitive functioning in children and comparison of the similarities to ASD symptoms.

POPs	Effects on children	Exposure Pathways	Target Organs	Similarity to ASDs symptoms	Reference
DDT	IQ deficits	Contaminated food and breast milk	Hypothalamus	High	Extension Toxicology Network (1996)
	Social-behavioral disability		Amygdaloid	High	
	Memory loss		Hippocampus	High	
PCBs	Memory loss	Dairy products and animal fat	Hippocampus	Very high	Winneke (2011)
	Mental retardation		Central nervous system	Somehow similar	
	Lack of concentration		Frontal lobe	Very high	
	Vomiting		Brain	Not clear	
	Slurred speech		Language center	High	
PBDEs	IQ deficits	Food, household dust and indoor air	Brain	Sometimes	Herbstman et al. (2010)
	Socio-behavioral disabilities		Amygdaloid	High	
	Decreased attention		Frontal lobe	Very high	
	Vomiting		Brain	Not clear	
	Slurred speech		Language center	High	

Studies in Faroe Islands, Germany, Holland, Michigan (USA), New York (USA), and Taiwan all revealed an inverse association between prenatal exposure to PCBs and cognitive outcomes during childhood or infancy cognitive functioning (Schantz et al., 2003). One prospective study in Michigan linked prenatal exposure to PCBs to abnormal neural development in children who were reported with significant decreases in full-scale and verbal IQ scores (Jacobson and Jacobson, 1996). An Oswego cohort investigated by Stewart et al. (2008) also showed lower IQ in school-age children linked with prenatal PCB exposure. Furthermore, a German study of 171 mother-child pairs reported that an increase in PCB levels in maternal milk from 173 to 679 ng/g lipids were associated with a 9.1 point decrement in the Bayley Scales of Infant Development mental scores, suggesting negative associations between prenatal and postnatal exposures to PCB via breastfeeding and mental/motor development during early childhood (Walkowiak et al., 2001).

Winneke (2011) suggested a plausibility for PCB-related neurodevelopmental adversity due to PCB induced thyroid dysfunction and oxidative stress. According to the results of their Düsseldorf study, PCB-related mental retardation and deficit in motor development were observed up to 40 months of age. These indicated that pre- and early postnatal exposure to environmental levels of PCBs is linked with mental retardation and motor development, and even pose adverse effects on maternal intelligence and development (AboutKidsHealth Canada, 2009). Therefore, PCBs exposure may adversely affect neurodevelopment and may, thus act as a contributor in the development of neurodevelopment disorders like autism (see Table 2).

2.2.3. Polybrominated diphenyl ethers (PBDEs)

PBDEs were included in the Stockholm Convention on POPs in 2009. They are commercially used as flame retardants at increased levels in home furnishings and electronics products (Messer, 2010). Humans and animals are at a high risk of PBDE exposures as the compounds have been commonly found in food, indoor air, and household dust. It is known that PBDEs are not chemically bound to products, therefore they can leach into the environment (Wong, 2013). PBDEs are suspected to interfere with the hormone systems by mimicking, blocking, or altering signaling of thyroid hormones and is thus considered an endocrine-disrupting chemical (Messer, 2010). Emerging evidence from animal studies has showed that prenatal and early life exposure to PBDEs may result in adverse neurodevelopmental effects. Alternations include hyperactive spontaneous behaviors, deficiency of memory and learning, and decreases in stimuli-responsive capability have been observed in rodents, which are comparable to the effects observed in humans (Hertz-Picciotto et al., 2011).

Furthermore, a longitudinal cohort of 329 mothers from Manhattan by Herbstman et al. (2010) resulted in an association between prenatal PBDE exposure and detrimental effects on neurodevelopment of their children at age of 12–48 and 72 months old. Children with higher cord blood concentrations of PBDE congeners 47, 99, and 100 were reported to have significant lower scores (−7.7, −9.3, and −10.9 points, respectively) in mental and physical development tests as compared to children of the same age (Herbstman et al., 2010) (see Table 2). These results suggest that PBDE might be a contributing factor for the development of neurodevelopmental disorders such as autism. On the other hand, a case-control epidemiological investigation called CHARGE (Childhood Autism Risk from Genetics and the Environment) reported that there is no significant difference between plasma PBDEs levels in children with autism/ASD, developmental delay, and typically developing controls (Hertz-Picciotto et al., 2011). However, this cannot preclude an etiological role for PBDEs in autism, as current PBDEs levels in blood samples are not representative of early life exposures, as PBDEs are easily released into food chains and from household products. Therefore, direct measurements of prenatal and early life exposures are required to explore the potential causal role in ASD (Hertz-Picciotto et al., 2011).

3. Emerging chemicals of concern and autism

Addressing the concerns of emerging chemicals is indeed a moving target because a vast quantity of chemicals has not been fully tested for their toxicity before commercialization and they may eventually pose a threat to the environment and cause adverse human health effects (Wong, 2013). For instance, in the U.S., there are currently 85,000 chemicals in commerce, about 2500 among them are high production volume (HPV) chemicals with an annual production rate of more than 450,000 kilograms (DTSC, 2007). However, insufficient toxicological examinations have been conducted to evaluate adverse effects of these HPV chemicals on animals and humans before they entered the market. Almost 45% of HPV chemicals are lacking of these tests and each year about 2000 new chemicals emerge at a rate of seven new chemicals per day in the U.S. (DTSC, 2007). Therefore, it is urgent to raise awareness about the health and environmental impacts of emerging chemicals of concern regarding their toxicity and persistence in the environment (Heritage Environmental Services, 2013). Recent studies have also shown that chemicals in this category can act as endocrine disrupters (EDs), such as bisphenol A (BPA) and phthalates, which not only produce effects at ppb and ppt levels in animals, but some can also produce transgenerational effects in many generations when the animals are exposed to emerging chemicals of concern in utero (DTSC, 2007). It has been revealed that emerging chemicals of concern such as PAEs and BPA are involved in the etiology of ASDs (Testa et al., 2012). This is because PAEs and BPA are EDs which can be transferred from mother to fetus or to

newborn across the placenta or through breastfeeding, respectively, and then may interfere with neurodevelopment in children (Mitchell et al., 2012; Testa et al., 2012).

3.1. Phthalates (PAEs)

Phthalates are widely used in various industrial sectors as plasticizer, solvents and additives in a number of consumer products, such as vinyl flooring, wall covering, food containers, cosmetics, coatings of pharmaceutical pills, and nutritional supplements for the purpose of enhancing their flexibility, transparency and durability (Schettler, 2006; Wong, 2013; Wormuth et al., 2006). As a member of EDs, phthalates exposure is suspected to be relevant to ASD pathogenesis due to their neurotoxicity (Testa et al., 2012).

Given that di 2-ethylhexy phthalate (DEHP) is an extensively used plasticizer in pharmaceutical and medical devices, Testa et al. (2012) evaluated primary and secondary metabolites of DEHP in 48 children with ASD and 45 control children and reported significantly higher urinary concentrations of mono-2-ethyl-5-hydroxyhexyl phthalate (5-OH-MEHP) (52.1%, median 0.18) and mono-2-ethyl-5-oxohexyl phthalate (5-oxo-MEHP) (46.0%, median 0.096) in patients with ASD as compared to the control group. In addition, a 91.1% specificity of 5-oxo-MEHP (fully oxidized form) was shown in identifying autistic patients. These findings demonstrated a linkage between phthalates exposure and ASD (Testa et al., 2012).

An inner-city (New York City) cohort study of 296 mother-child pairs recorded reduced physical development among children at 3 years of age, whose mothers had higher urinary di-butyl phthalate (DBP) metabolite concentrations during pregnancy and gestation (Whyatt et al., 2009). A more recent prospective study of 277 mother-child pairs by Whyatt et al. (2012) also showed similar results, with lower mental and motor development scores as well as increased withdrawn and internalizing behaviors at 3 years of age among children born to mothers with higher prenatal urinary phthalate metabolite concentrations [i.e. mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), monoisobutyl phthalate (MiBP)]. More specifically, increasing log MnBP and log MiBP concentrations were linked with decreased child Psychomotor Development Index (PDI) scores, i.e. [estimated adjusted β-coefficient = −2.81; 95% confidence interval (CI): −4.63, −1.0] and (β = −2.28; 95% CI: −3.90, −0.67), respectively. Mental Development Index (MDI) scores also reduced with rising log MnBP (β = −2.67; 95% CI: −4.70, −0.65) in girls. In addition, children born to women with higher MnBP and MBzP exposures were 2.2 and 1.5 times more likely to develop clinical withdrawn behaviors, respectively. The risk of developing clinically significant internalizing behaviors were also reported to increase by 1.3–1.4 times in children whose mothers had higher MBzP exposure (Whyatt et al., 2012). Furthermore, these two studies suggested a negative correlation between prenatal phthalate exposure and child physical/mental/motor development.

Table 3 shows two studies related to human beings that link phthalates exposure with ASD. Engel et al. (2010) examined 188 children from New York City for their cognitive and behavioral development at 4–9 years of age upon prenatal exposure to phthalate exposure. Poor scores on the aggression, attention problems, depression, externalizing problems, and behavioral symptoms index were reported to be linked with increased concentrations of maternal prenatal urinary low molecular weight (LMW) phthalate metabolites. A consistent association was also demonstrated between LMW phthalate metabolites and executive functioning (Table 3). These results suggested that prenatal exposure to LMW phthalate may induce autism-like behaviors and affect neurodevelopment in children (Table 3). A more recent study by Stein et al. (2013) reported a decreased efficiency for detoxification of DEHP metabolites through glucuronidation in children with ASD, suggesting a potential mechanism that may correlate phthalate exposure with ASD development.

These findings consolidate the potential link between childhood phthalate exposures and ASD pathogenesis based on the evidence that phthalates exposure caused autism-like behavior changes and neurodevelopment alternations in human beings.

3.2. Bisphenol A (BPA)

Bisphenol A is another emerging chemical of concern that has been believed to be involved in the etiology of ASD. It is a common plasticizer, commonly used in production of polycarbonate plastics, polyvinyl chloride (PVC), and the epoxy resins (Stein et al., 2015). Humans can be easily exposed to BPA through contact with plastics, plastic-wrapped foods, drinking water, and inhalation of contaminated indoor air (Erickson, 2008). Biomonitoring studies indicate that more than 90% of the populations have detectable levels of BPA in different biological matrices (Mustieles et al., 2015).

Furthermore, increased maternal exposure to BPA has been revealed by epidemiological studies associated with behavioral difficulties in children. A Swedish study examined 4779 eligible children and 72 who were parentally reported with ASD. Five statistically significant variables associated with autism were found which included PVC flooring material (Larsson et al., 2009). Stein

Table 3
Studies linking phthalates exposure and autism in children.

Exposure Phthalates	Study population	Detected urine phthalate concentrations	Induced behavioral changes	Induced neurotoxicity	Reference
Low molecular weight (LMW) phthalate metabolites	177 mothers and 188 children	No data available	Lack of focus Slurred language	Non or not full development of neuro-system Alternation of the maternal thyroid hormone system	Engel et al. (2010)
Diethylhexyl phthalate (DEHP)	55 children with ASD and 53 age-matched controls	Total median MEPH[a] = 10.96 ppt Total median 5-OH MEHP[a] = 5.79 ppt Total median 5-oxo MEHP[a] = 3.33 ppt Total median 5-cx MEPP[a] = 238.5 ppt	Mental retardation Memory loss Hemostatic problems	Mental disorders	Stein et al. (2013)

[a] MEHP monoethylhexylphthalate, 5-OH MEHP 5-hydroxy-methylethylhexyl phthalate, 5-oxo MEHP 5-oxo-methylethylhexyl phthalate, 5-CX MEPP 5-carboxy-methylethylhexyl phthalate.

Table 4
Human epidemiological studies liking bisphenol A (BPA) and children neurobehavior (adopted from Mustieles et al., 2015).

Study Population	Urine BPA concentration	Neurobehavior effect	Authorship-Study design
244 mother-child pairs	**Maternal gestational total BPA** (16 wk, 26 wk and birth): 2 ng/ml **Childhood total BPA:** 4.1 ng/ml	**Gestational BPA exposure:** -Girls: positive associations found **Childhood BPA exposure:** no associations found	Braun et al. (2011)
198 mother-child pairs	**Maternal gestational total BPA** (34 wk; range 24–40 wk): 1.96 ng/ml **Childhood total BPA** (between 3 and 4 years): 3.94 ng/ml	**Gestational BPA exposure:** -Boys: increased emotional reactivity and aggressive behavior -Girls: decreased anxiety and less aggression **Childhood BPA exposure:** negative association found only for the Emotionally Reactive scale within all sampled children	Perera et al. (2012)
292 mother-child pairs	**Maternal gestational total BPA** (13.6 wk and 26.4 wk): 1.1 ng/ml **Childhood total BPA** (at 5 years): 2.5 ng/ml	**Gestational BPA exposure** -Boys: higher BPA concentrations during pregnancy associated with increased internalizing problems, increased anxiety, depression and aggression -Girls: no associations found **Childhood BPA exposure:** -Boys: increased anxiety, depression and inattention -Girls: associations found with increased anxiety, depression, externalizing (hyperactivity and conduct problems)	Harley et al. (2013)

et al. (2015) evaluated urine BPA levels in 46 autistic children and 52 controls. The results showed that about 20% autistic patients were detected with BPA levels exceeding 90th percentile (>50 ng/ml) of the frequency distribution. BPA metabolites and total BPA concentrations were found to be three times higher in the ASD group than the controls ($P < 0.001$). Furthermore, exposure to BPA is also found to be linked with increased oxidative stress and mitochondrial dysfunction in the lymphoblasts, which was demonstrated by a rise in the production of free radicals and a drop in mitochondrial membrane potential in both autism and control groups. In addition, a significant higher level of reactive oxygen species (ROS) was reported in the autism group as compared to the control group (Mustieles et al., 2015).

In addition, the biological plausibility of the adverse effects of BPA on the brain has been noted in three epidemiology studies (Table 4). Exposure to environmental BPA have been demonstrated to result in altered neurobehavior including aggressive behavior, attention deficit, and hyperactivity, mostly found in children exposed in utero, indicating that prenatal exposure may be linked to adverse neurobehavioral functioning in children (Mustieles et al., 2015).

4. Airborne pollutants and autism

A systematic review and meta-analysis was carried out by Lam et al. (2016) and results showed that early life exposure to air pollution may contribute to a diagnosis of ASD, and exposure to particulate matter (PM_{10} and $PM_{2.5}$) provided the strongest evidence to support an association between exposure to air pollutants and ASD. In this review, six robust studies were utilized (five case-control and one cohort) for the meta-analysis with minimal risk of bias concerns and involved a total of 9557 children with autism and 143,997 controls.

Particulate pollutants, in particular $PM_{2.5}$ are able to penetrate deep into the lungs and can enter blood circulation, where they can induce oxidative stress resulting in perturbation of neurodevelopment (Grahame et al., 2014). A number of studies indicated associations between traffic-related and criteria air pollutants and the development of ASD and the possibility of increased susceptibility with such exposure during late pregnancy or early postnatal life.

5. Chemicals management issues

Global actions have been set into motion, for instance, the United Nations Environment Programme (UNEP) and Global Environment Facility (GEF) commissioned a review on "Emerging chemicals issues in developing countries and countries with economy in transition". This study aimed to identify a number of emerging chemicals of concern to fulfill GEF's immediate goal of maximizing the effectiveness of chemical lifecycle management and minimizing significant adverse effects exerted by these chemicals on human and global health (Bouwman et al., 2012). The US Environmental Protection Agency (EPA) is currently working on their list of CEC and some emerging chemicals of global concern have been identified, which include BPA, PAEs, pharmaceuticals, and personal care products (Heritage Environmental Services, 2013; Bouwman et al., 2012).

6. Conclusion

The worldwide increase in prevalence of ASDs has produced exponential interest towards environmental toxicants that impact human health. These environmental pollutants include heavy metals (Hg and Pb), POPs (DDT, PCBs and PBDEs), and emerging chemicals of concern (PAEs and BPA), which are suggested as contributing factors in the development of ASD as revealed by an increasing number of studies that focus on evaluating adverse effects of these toxicants on the neurodevelopment in children. Major windows of neurodevelopment vulnerability associated with neurotoxic chemicals exposure occur during the fetal period, infancy and early childhood, which may result in permanent damage to brain of children.

Many studies have reported that prenatal exposure to environmental toxicants via maternal exposure to environmental pollutants could lead to cognitive deficits and neurobehavioral changes in children that are similar to traits of ASD, suggesting their potential etiological roles in ASD. However, limitations are present in these studies which include relatively small subject size, lack of direct evidence, retrospective design and limited understanding of possible mechanisms linking these toxicants with ASD. More in-depth research and effort such as more high-quality epidemiological studies are needed to investigate the link between environmental factors and ASD.

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