Environmental Research 151 (2016) 493–504

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

The role of phthalate esters in autism development: A systematic review

Maryam Zare Jeddi [a], Leila Janani [b], Amir Hossein Memari [c], Shahin Akhondzadeh [d], Masud yunesian [a,e,*]

[a] Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
[c] Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[d] Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
[e] Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 14 February 2016
Received in revised form
29 July 2016
Accepted 17 August 2016

Keywords:
Children with autism
Developmental disorder
Environmental risk factors
Phthalate esters
Endocrine disruptors

ABSTRACT

Background: Available evidence implicates environmental factors in the pathogenesis of autism spectrum disorders (ASD). However, the role of specific environmental chemicals such as phthalate esters that influence ASD risk remains elusive. This paper systematically reviews published evidences on association between prenatal and/or childhood exposure to phthalate and ASD.
Methods: Studies pertaining to systematic literature search from Scopus, PubMed, PsycInfo and Web of Science prior to December 2015 were identified. The authors included studies which assessed the effect of exposure to phthalates on occurrence of ASD. This comprehensive bibliographic search identified five independent studies. Each eligible paper was summarized with respect to its methods and results with particular attention to study design and exposure assessment. Because of the heterogeneity in the type of included studies, different methods of assessing exposure to phthalates and the use of different statistics for summarizing the results, meta-analysis could not be used to combine the results of included studies.
Results: The results of this systematic review have revealed the limited number of studies conducted and assessed phthalate exposure. Seven studies were regarded as relevant to the objectives of this review. Two of them did not measure phthalate exposure directly and did not result in quantitative results. Out of the five studies in which phthalate exposure was mainly measured by the examining biomarkers in biological samples, two were cohort studies (one with positive results and another one with not clear association). Among the three case control studies, two of them showed a significant relation between exposure to phthalate and ASD and the last case control study had negative results. Indeed, this case control studies showed a compromised phthalate metabolite glucuronidation pathway, as a probable explanation of mechanism of the relation between phthalate exposure and ASD.
Conclusions: This review reveals evidence showing a connection between exposure to phthalates and ASD. Nevertheless, further research is needed with appropriate attention to exposure assessment and relevant pre and post-natal cofounders.

Contents

* Corresponding author at: School of Public Health, Tehran University of Medical Sciences, Pour sina St., Enqelab Sq., Tehran 1417653761, Iran.
E-mail address: yunesian@tums.ac.ir (M. yunesian).

http://dx.doi.org/10.1016/j.envres.2016.08.021
0013-9351/

1. Introduction

Since the industrial revolution, synthetic chemicals have been increasingly manufactured in order to be used in almost every product with which we are in contact. From a scientific perspective, recent data have shown that nearly all the people regardless of age and sex are being exposed to hundreds of these man-made chemicals worldwide (Meeker, 2012). It has been proved that nearly two hundreds of these chemicals are neurotoxic in humans; and even worse , based on laboratory analysis, more than 1000 of such compounds can potentially be neurotoxic (Schwartzer et al., 2013). However, less than 20% of high-volume chemicals have been screened for potential neurodevelopmental toxicity during early development (Landrigan, 2010). It should be noted that human brain, at its early developing stage, is highly vulnerable and sensitive to the damages caused by environmental neurotoxicants. In fact, exposure of the brain to neurotoxicants at this stage could damage this vital organ in a way which is far worse than what it does to an adult brain (Grandjean and Landrigan, 2006; Weiss, 2000). This susceptibility roots from the fact that during the 9 months of prenatal life, the human brain develops from a strip of cells along the dorsal fetal ectoderm into a complex organ consisting billions of precisely located, highly interconnected and specialized cells. In fact, exposure to environmental chemicals, especially endocrine disruptor chemicals (EDCs), during the brain growth spurt (BGS) in prenatal period, has been suggested to be a possible causal factor for neurodevelopmental disorders (Colborn, 2004; Kim et al., 2010). In this regard, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) could be the outcomes of exposure to these chemicals (Miodovnik, 2011; Tanida et al., 2009). The BGS period usually begins during the third trimester of pregnancy and continues throughout the first two years of life (Kim et al., 2010). Although the involvement of genetic abnormalities in developing ASD is well-accepted, it is widely believed that a single genetic risk factor cannot cause ASD. In other words, the most likely cause of ASD might be genetic susceptibility besides the exposure to environmental neurotoxic compounds (Hertz-Picciotto et al., 2006). In fact, this hypothesis provides a plausible explanation for the rapid increase in the incidence of ASD over the past few decades (Hertz-Picciotto and Delwiche, 2009).

ASDs are comprised of a broad spectrum of heterogeneous, neurodevelopmental disorders (Ashwood et al., 2006). Previously, disorders which were considered as part of the autism spectrum were divided into the following discrete categories: Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The DSM-V, published in May 2013, combined the previous categorical disorders into a single category of “Autism Spectrum Disorder,” with varying degrees of severity depending on the amount of support required by an individual. Because no medical or biological marker exists for ASD, the diagnosis is mostly based on behaviors (APA, 2013). Thus ASD, similar to the one first described in 1943 by Kanner, is a complex developmental disability with social, cognitive, and communicative deficits (Kanner, 1943). The symptoms of autism usually appear before a child reaches the age of three and last throughout the life (CDC, 2012). From a social point of view, some children with ASD have difficulty in understanding the fact that others think differently from the way they do, and in coordinating attention with a social partner. Regarding the cognitive deficit, some children have weak central coherence and executive dysfunction and these continue into adulthood in some individuals (Mendes, 2013).

In a scientific statement published by the Endocrine Society in 2009, it was argued that endocrine disruptors indeed pose a “significant concern for public health”(Diamanti-Kandarakis et al., 2009). Recently, due to proven adverse effects on human health, concerns over a class of chemicals namely, phthalates has also emerged (Myers, 2012). Phthalates with a di-ester structure are additive polymers applied as plasticizers to produce high volumes of synthetic chemicals (Miodovnik et al., 2014a). In fact, these chemicals are being used to provide flexibility, durability, and solubility and can be found in a wide range of products used in daily life (Lyche et al., 2009); many of these products do not require labeling of phthalates as an ingredient (Dodson et al., 2012). Currently, over a dozen forms of phthalates are in commerce among which di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), butylbenzyl phthalate (BBP or BBzP), diisoheptyl phthalate (DiHP), di-n-butyl phthalate (DBP or DnBP) and diethyl phthalate (DEP) are the most commonly produced forms (Miodovnik et al., 2014a). Concerns over human exposure to phthalates root from the fact that these compounds do not form a covalent bound with the polymer matrix. In other words, phthalates may leach or outgas into their surroundings. Humans are exposed to phthalates via ingestion, inhalation and dermal exposure during their whole lifetime including intrauterine development. (Heudorf et al., 2007; Zare Jeddi et al., 2015). In fact, it is not surprising that metabolites of some phthalates can be detected in saliva, urine, amniotic fluid and breast milk (Fromme et al., 2007; Koch et al., 2006; Koch et al., 2011; Völkel et al., 2014). Since, the potential consequences of human exposure to phthalates have raised