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Environmental Chemical Substances in Relation to Neurodevelopmental Disorders: A Systematic Literature Review

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1. Introduction

Since the 1950s-70s, increasing number of regulations have rapidly expanded for the global usage of industrial, agricultural and other environmental chemical substances (ECSs). It is believed that children are at high risk of exposure to ECSs, which are produced in quantities greater than one million tons per year and widely dispersed in air, water, food crops, communities, waste sites and homes (Landrigan et al. 2006). Prevalence rates of many common diseases in children, including certain childhood cancers (Devesa et al. 1995; Robison et al. 1995; Schechter 1999; Supriyadi et al. 2011), birth defects (Ananth et al. 2005; Gilboa et al. 2010) and neurodevelopmental disorders (Malik et al. 2011), have been increased or maintained at high levels in industrialized countries. Although primary etiologic factors contributing to these diseases are unknown yet, accumulating evidences indicate that exposure to ECSs are partially responsible for the developmental disabilities, such as autism spectrum disorders (ASDs), attention deficit hyperactivity disorder (ADHD), and other developmental delays (Boyle et al. 2011; Larson et al. 2001) (Figure 1). In this chapter, we conducted a systematic literature review for neurotoxic agents in environment to elucidate the relationship between exposure to ECSs and neurodevelopment disorders in children.

2. Exposure to ECSs and neurodevelopmental disorders in children

According to the Fourth National Report on Human Exposure to Environmental Chemicals (Fourth Report), 212 ECSs were detected in the urine and blood samples from the civilian, noninstitutionalized U.S. population (CDC 2009). Therefore, we searched literatures for these 212 ECSs with keywords of "learning disabilities", "developmental delay" and "autism" by PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), and then a total of 1075 literatures were selected published during 1972 - 2011 July. These ECSs were categorized by their chemical features in this review (Table 1). Neurodevelopmental disorders in children are disabilities associated primarily with the functionings of the neurological system and brain, which include ADHD, ASDs, mental retardation (MR) and learning disabilities (LD). It has been known that children with neurodevelopmental disorders experience problems

with language and speech, motor skills, behavior, memory, learning, or other neurological functions. Therefore, we further selected important papers by the review of the keywords, such as children, exposure, neurobehavioral, neurotoxicity, neuropsychological, disabilities, cognitive, development, behavior and school-aged for human study and learning memory, exposure, neurobehavioral, neurodegeneration, neurogenesis, neuropathological, neurotoxicity, impairments, deficits, behavior, hippocampus, developmental, cognitive, disorders, receptors and model for animal studies. Here, a total of 142 literatures for human study (Table 2) and 168 literatures for animal experiments were listed (Table 3).

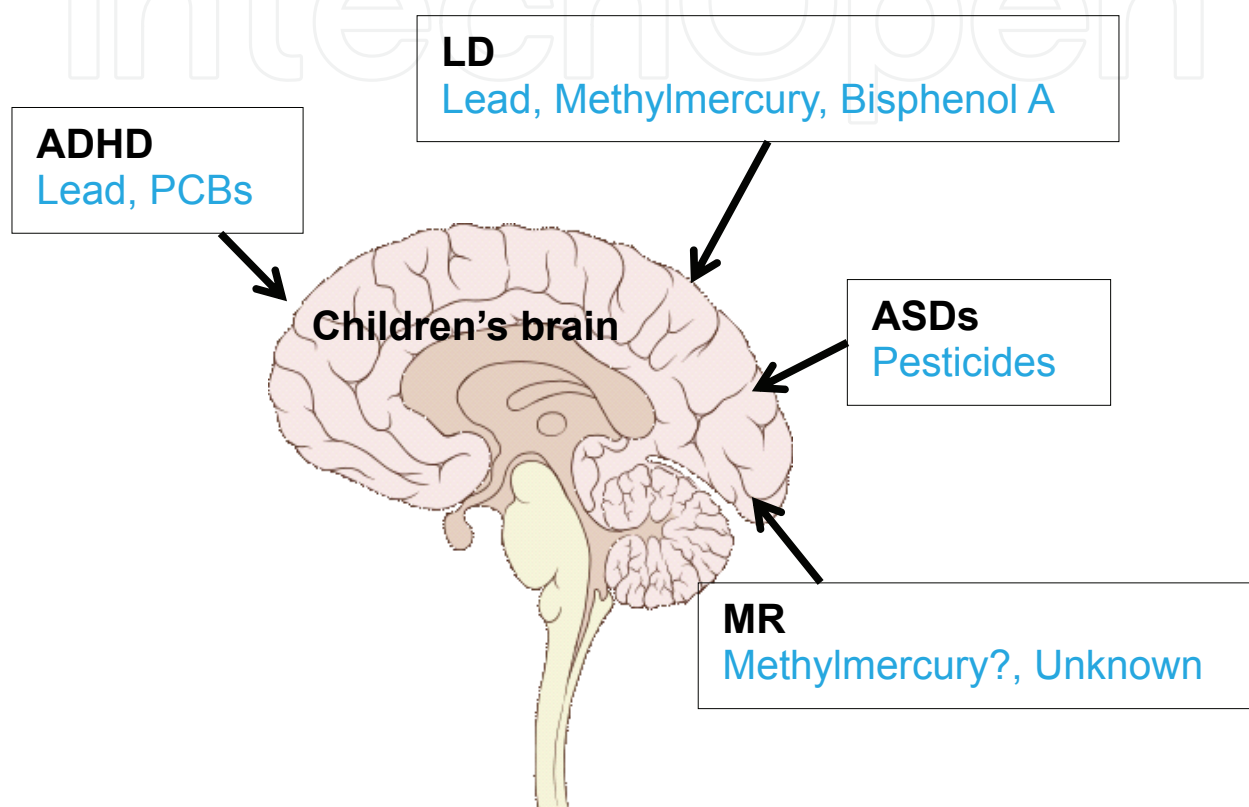


Fig. 1. Relationship between ECSs and neurodevelopmental disorders in children. ADHD: attention deficit hyperactivity disorder, LD: learning disability, ASDs: autism spectrum disorders, MR: mental retardation.

Categories	Chemical substances
<u>Metals</u>	Antimony, Arsenic, Dimethylarsinic Acid, Monomethylarsonic Acid, Trimethylarsine oxide, Barium, Beryllium, Cadmium, Cobalt, Lead, Mercury, Molybdenum, Platinum, Thallium, Tungsten, Uranium
<u>Particulate matters and smoke</u> Particulate matters	PM10, PM2.5, Carbon monoxide (CO) Sulfur dioxide (SO ₂), Nitrogen oxides (NO _x), Ozone (O ₃), Asbestos
Smoking	Cotinine, NNAL(4-methylnitrosamino)-1-(3-pyridyl)-1-butanol)

Categories	Chemical substances
<u>Agricultural related chemicals</u> Herbicides and metabolites	Acetochlor mercapturate, Alachlor mercapturate, Atrazine mercapturate, 2,4-Dichlorophenoxyacetic acid, Metolachlor mercapturate, 2,4,5-Trichlorophenoxyacetic acid, N,N-Diethyl-meta -toluamide (DEET)
Insecticides and metabolites	Carbamates, Carbofuranphenol, 2-Isopropoxyphenol
Organochlorines and metabolites	Aldrin, o,p' -Dichlorodiphenyltrichloroethane, p,p' -Dichlorodiphenyltrichloroethane (DDT), p,p' -Dichlorodiphenyldichloroethene (DDE), Dieldrin, Endrin, Hexachlorobenzene, beta -Hexachlorocyclohexane, gamma-Hexachlorocyclohexane (Lindane), Heptachlor epoxide, Mirex, trans -Nonachlor, Oxychlorane, 2,4,5-Trichlorophenol, 2,4,6-Trichlorophenol
Organophosphorus insecticides: dialkyl phosphate metabolites	Diethylphosphate (DEP), Dimethylphosphate (DMP), Diethylthiophosphate (DETP), Dimethylthiophosphate (DMTP), Diethyldithiophosphate (DEDTP), Dimethyldithiophosphate (DMDTP)
Organophosphorus insecticides: specific insecticides and metabolites	3-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one/ol, 2-(Diethylamino)-6-methylpyrimidin-4-ol/one, 2-Isopropyl-4-methyl-6-hydroxypyrimidine, Malathion dicarboxylic acid, para -Nitrophenol, 3,5,6-Trichloro-2-pyridinol
Pyrethroid pesticide metabolites	cis -3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid, cis -3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, trans -3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 4-Fluoro-3-phenoxybenzoic acid, 3-Phenoxybenzoic acid
<u>Persistent organic pollutants</u>	
Perfluorinated compounds	Perfluorobutane sulfonic acid (PFBS), PFDeA, PFDoA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFUA
Polybrominated diphenyl ethers and polybrominated biphenyl	2,2',4-Tribromodiphenyl ether (BDE 17), BDE 28, BDE 47, 2BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, 2,2',4,4',5,5'-Hexabromobiphenyl (BB 153)

Categories	Chemical substances
Polychlorinated biphenyls, non-dioxin-Like	PCB 28, PCB 44, PCB 49, PCB 52, PCB 66, PCB 74), 2,2',3,4,5'- PCB 87, PCB 99, PCB 101, PCB 110, PCB 128, PCB 138 , PCB158, PCB 146, PCB 149, PCB 151, PCB 153, PCB 170, PCB 172, PCB 177, PCB 178, 2,2',3,4,4',5,5'- PCB, 180 PCB 183, PCB 187, PCB 194, PCB 195, PCB 196, PCB 203, PCB 199, PCB 206, PCB 209
Dioxin-like polychlorinated Biphenyls Coplanar polychlorinated biphenyls Mono-ortho-substituted polychlorinated biphenyls	PCB 81, PCB 126, PCB 169 PCB 105, PCB 118, PCB 156, PCB 157, PCB 167, PCB 189, 1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF), 1,2,3,4,7,8,9-
Polychlorinated dibenzofurans	HpCDF, HxCDF, HxCDF, HxCDF, HxCDF, OCDF, 1PeCDF, PeCDF, TCDF
Polychlorinated dibenzo- <i>p</i> -dioxins	2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin (TCDD), HpCDD, HxCDD, HxCDD, HxCDD, OCDD, PeCDD,
Polycyclic aromatic hydrocarbon metabolites	2-Hydroxyfluorene, 3-Hydroxyfluorene, 9-Hydroxyfluorene, 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol), 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 1-Hydroxypyrene
Volatile organic compounds (VOCs)	Benzene, Chlorobenzene, 1,2-Dibromo-3-chloropropane, Dibromomethane, 1,2-Dichlorobenzene, m-Dichlorobenzene, Paradichlorobenzene, 1,1-Dichloroethane, Ethylene dichloride, Vinylidene chloride, cis -1,2-Dichloroethene, trans -1,2-Dichloroethene, Dichloromethane, 1,2-Dichloropropane, 2,5-Dimethylfuran, Ethylbenzene, Hexachloroethane, Methyl tert -butyl ether (MTBE), Nitrobenzene, Styrene, 1,1,2,2-Tetrachloroethane, Perchloroethylene, Carbon tetrachloride, Toluene, Methyl chloroform, 1,1,2-Trichloroethane, Trichloroethene Trichloroethylene, o -Xylene, m- and p -Xylene

Categories	Chemical substances
<u>Hormones and environmental hormones (endocrine disrupting chemicals)</u> Environmental phenols	Bisphenol A (2,2-bis [4-Hydroxyphenyl] propane), Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone, 4-tert -Octylphenol (4-[1,1,3,3-Tetramethylbutyl] phenol) , Triclosan (2,4,4'-Trichloro-2'-hydroxyphenyl ether)
Phthalate metabolites	Mono-benzyl phthalate (MBzP), MiBP, MnBP, MCHP, MEP, MEHP, MEHHP, MEOHP, MECPP, MiNP, MMP, MCPP, MOP
Phytoestrogens and Metabolites	Daidzein, O-Desmethylangolensin, Enterodiol, Enterolactone, Equol, Genistein
<u>Other combustion products and by-products</u> Acrylamide Adducts	Acrylamide, glycidamide
Chloromethane related by-Products	Bromodichloromethane, dibromochloromethane (chlorodibromomethane), Tribromomethane (bromoform), Trichloromethane (chloroform)

Table 1. List of ECSs detected in human blood and urine that has been related with LD.

2.1 Association between ECSs exposure with LD

Studies have found that several widespread environmental contaminants can damage the children's developing brains and nervous systems. In our literature review, lead, methylmercury, pesticides, tobacco (cotinine), persistent organic pollutants such as polychlorinated biphenyls (PCBs), and environmental hormones such as bisphenol A and phthalates have been indicated association between neuronal disability and exposure levels in children (Table 3). For instances, prenatal tobacco and childhood lead exposures may be significant risk factors for ADHD, especially when individuals are exposed to both of these toxicants (Froehlich et al. 2009). Although the U.S. has made considerable strides in reducing these toxicant exposure, 15% of women reported smoking during pregnancy in the U.S. population-based study in 2004 (Allen et al. 2008), and an estimated 1.6% of U.S. children showed blood lead levels of concern ($\geq 10 \mu\text{g}/\text{dL}$) in 1999–2002, with almost 14% having levels of 5 to 9 $\mu\text{g}/\text{dL}$ (CDC 2005). These findings suggest that reduction of toxicant exposure may be an important role for the preventions of ADHD as well as other neurodevelopmental disorders in children.

In addition, the accumulating evidences suggest a link between lead exposure and memory impairment. van Wijngaarden *et al.* (2009) conducted a pilot study of 47 healthy subjects aged 55–67 years to examine associations between bone lead levels and 4 tests sensitive to the natural history of Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD), which included 3 subtests of the Cambridge Neuropsychological Test Automated Battery (delayed match-to-sample, paired associates learning and spatial recognition memory) and

the Montreal Cognitive Assessment Test. By measurements of bone lead concentrations, higher tibial and calcaneal bone lead values were significantly ($p < 0.05$) associated with lower performance levels on delayed match-to-sample and paired associates learning in unadjusted analyses with Spearman rank correlation coefficients of about 0.4. Multiple linear regression analyses (i.e., least-squares means of cognitive test scores across tertiles of lead exposure) adjusted for age, education and smoking status continued to show an association of higher calcaneal lead levels with increasing memory impairments on delayed match-to-sample ($p = 0.07$). As might be expected, additional adjustment for history of hypertension reduced the strength of this association ($p = 0.19$). Given the demonstrated impact of lead exposure on hypertension and the vascular aetiology of certain dementias, authors speculated that hypertension could play a mediating role in the association between lead exposure and memory impairment.

Pesticides and their degradation products are ubiquitous in the environment. The most commonly detected indoor pesticides (organophosphates and pyrethroids), which are routinely applied in classrooms and playgrounds, are well-known neurotoxicants that affect the ability to learn and process information (Tulve et al. 2006). In our literature survey, Xu *et al.* (2011) examined the association between body burden of trichlorophenol (TCP) (ie, 2,4,5-TCP and 2,4,6-TCP) and ADHD by logistic regression analyses using data from the 1999–2004 National Health and Nutrition Examination Survey (NHANES) to evaluate the association between urinary TCPs and parent-reported ADHD among 2546 children aged 6–15 years. Their results showed that children with low levels ($< 3.58 \mu\text{g/g}$) and high levels ($\geq 3.58 \mu\text{g/g}$) of urinary 2,4,6-TCP had a higher risk of parent-reported ADHD compared to children with levels below the limit of detection (OR 1.54, 95% CI 0.97 to 2.43 and OR 1.77, 95% CI 1.18 to 2.66, respectively; p for trend = 0.006) after adjusting for covariates. No association was found between urinary 2,4,5-TCP and parent-reported ADHD. These results suggested that exposure to TCP may increase the risk of behavioural impairment in children, especially in countries where organochlorine pesticides are still commonly used. It also should be noted that Rauh *et al.* (2006) reported the impact of prenatal exposure to chlorpyrifos on 3-year neurodevelopment and behavior in city-residential minority 254 children. The report examined cognitive and motor development with the Bayley Scales of Infant Development II and child behavior with the Child Behavior Checklist and chlorpyrifos levels in umbilical cord plasma. Highly exposed children (chlorpyrifos levels of $> 6.17 \text{ pg/g}$ plasma) scored, on average, 6.5 points lower on the Bayley Psychomotor Development Index and 3.3 points lower on the Bayley Mental Development Index at 3 years of age compared with those with lower levels of exposure. Children exposed to higher in compared with lower chlorpyrifos levels were also significantly more likely to experience Psychomotor Development Index and Mental Development Index delays, which are attention problems, ADHD problems, and pervasive developmental disorder problems at 3 years of age. The proportion of delayed children in the high-exposure group, compared with the low-exposure group, was 5 times greater for the Psychomotor Development Index and 2.4 times greater for the Mental Development Index.

It was also reported that children prenatally exposed to PCBs might be related with lowered intelligence and behavioral deficits. Relationships between adverse health effects and PCB exposure during infancy and childhood have been examined. Although some inconsistencies in the literature exist, the overall evidence supports a concern for adverse

effects of PCBs on children's neurological development. It should be noted that adverse effects on intelligence and behavior have been found in girls who were highly exposed to mixtures of PCBs, chlorinated dibenzofurans, and other pollutants prior to conception (Chen et al. 1992; Chen et al. 1994).

Chemicals	Study type/hazard effects	References
Arsenic	Encephalopathy: an uncommon manifestation of workplace arsenic poisoning?	Morton and Caron 1989
Arsenic	Neuropsychological impairment following inorganic arsenic exposure	Bolla-Wilson and Bleecker 1987
Cobalt	Hair element content in learning disabled children	Pihl and Parkes 1977
Cobalt	Evidence for interactions of lithium with vitamin B12 and with other trace elements	Schrauzer et al. 1992
Copper	Dose-effect relationships	Bowler et al. 2007
Copper	Hair mineral analysis and behavior: an analysis of 51 studies	Rimland and Larson 1983
Copper	Manganese inhibits NMDA receptor channel function: implications	Guilarte and Chen 2007
Copper	Poor cognitive development and abdominal pain: Wilson's disease	Gronlund et al. 2006
Copper, Zinc	Brain and behavior	Pfeiffer and Braverman 1982
Copper, mercury	School children	Capel et al. 1981
Lead, arsenic	Two metals, ADHD	Calderon et al. 2001
Lead	The Edinburgh Lead Study	Thomson et al. 1989
Lead	Cognition in children and very low lead exposure	Minder et al. 1998; Surkan et al. 2007
Lead, smoke	verbal memory, ADHD	Bleecker et al. 2005; Braun et al. 2006
Lead	Preschool children	Bellinger et al. 1987; Bellinger et al. 1991; Benetou-Marantidou et al. 1988; Fergusson et al. 1997; Jusko et al. 2008; McMichael et al. 1988; Mendelsohn et al. 1998; Rabinowitz et al. 1992; Stokes et al. 1998; (Schwartz et al. 2000; Ris et al. 2004; Shih et al. 2006; Schwartz et al. 2007; van Wijngaarden et al. 2009 ; Mahmoudian et al. 2009

Chemicals	Study type/hazard effects	References
Lead	School children (ADHD, learning disabilities)	Fergusson and Horwood 1993; Lyngbye et al. 1990; Tong et al. 1996; Tuthill 1996; Leviton et al. 1993; Minder et al. 1994; Buchanan et al. 1999; al-Saleh et al. 2001; Lanphear et al. 2005; McMichael et al. 1988; Canfield et al. 2003; Chiodo et al. 2007; Counter et al. 2008; Nigg et al. 2008; Schnaas et al. 2006; Wang et al. 2002; Wang et al. 2008; Kim et al. 2010
Lead, mercury, PCB	Children study three chemicals	Stewart et al. 2006
Mercury	infant immunizations	Redwood et al. 2001
Mercury	Children study	Grandjean et al. 1997; Schettler 2001; Counter et al. 2005; Johansson et al. 2007; Dufault et al. 2009; Valent et al. 2011
Mercury	Adult exposure	Yokoo et al. 2003
Mercury	Workers	Piikivi and Hanninen 1989; Counter et al. 2005
Molybdenum	A case report	Momcilovic 1999
Phosphorus-31 magnetic	Children study	Moss et al. 1997
Carbon monoxide	Children study	Binder and Roberts 1980
Carbon monoxide	Workers	Deschamps et al. 2003; Katirci et al. 2011
Cotinine	Adult Patients study	Smith et al. 2009
Smoking	Children study	Marshall et al. 1995; Robertson and Jackson 1996 Lassen and Oei 1998; Rowland et al. 2002; Batstra et al. 2003; Najman et al. 2004; O'Brien et al. 2004; Matsumoto et al. 2005; Uzun and Kendirli 2005b; Kukla et al. 2008; Petry et al. 2008; Kargoshaie et al. 2009; Anderko et al. 2010; DeGarmo et al. 2010; Freire et al. 2010; O'Callaghan et al. 2010
Smoking	Adolescent student study	Ivanovic et al. 2000; Molina and Pelham 2001; Kalyva 2007; Keselyak et al. 2007; Wang et al. 2009b
Pesticide	A case study.	Reidy et al. 1994
Pesticide	Children study	Stephens et al. 1995; Schettler 2001; Kofman et al. 2006; Rauh et al. 2006; Xu et al. 2011
Pesticide	Workers	Srivastava et al. 2000

Chemicals	Study type/hazard effects	References
DDT	Children study	Christenson et al. 2001; Griffin et al. 1993; Aase et al. 2006; Christenson et al. 1991; Dorner and Plagemann 2002; Sharma et al. 2009
Dioxin	Children study	van den Hazel et al. 2006; Lee et al. 2007
Formaldehyde	Children study	Madrid et al. 2008
Formaldehyde	Workers	LoSasso et al. 2001
PCBs	Children study	Chen et al. 1992; Chen et al. 1994; Roegge and Schantz 2006; Lin et al. 2010
Polyaromatic hydrocarbon	Children study	Sheng et al. 2010
Polychlorinated biphenyl	Children study	Sandberg et al. 2003; Lin et al. 2008
Polycyclic aromatic hydrocarbon	Children study	Walhovd et al. 2007; Bandstra et al. 2010; van Elderen et al. 2010
Phenol	Children study	Gross et al. 1987; Hertz-Picciotto et al. 2011
Industrial solvents	Children study	Uzun and Kendirli 2005a; Dick et al. 2010
Industrial solvents	Workers	Hanninen et al. 1976; Ryan et al. 1988; Moen et al. 1990; Morrow et al. 1992; Stollery and Flindt 1988; Bowler et al. 2001; LoSasso et al. 2001; Morrow et al. 2001; LoSasso et al. 2002

Table 2. Literature lists for the hazard effects of ECSs on human memory and cognition.

2.2 Possible mechanism of ECSs-induced autism and developmental delay

As above mentioned, several ECSs have been related with developmental delay such as ADHD and LD in human studies. However, little is known about the underlying mechanism by which ECSs could induce developmental delay. Animal experiments and *in vitro* studies using cells are useful to elucidate these kinds of mechanisms and understand the results of human studies. Animal studies listed in Table 3 indicate that most attentions have been focused on lead, mercury, pesticides and polycyclic aromatic hydrocarbons (PAHs). For example, toxic properties of lead have been attributed to its capability to mimic calcium and alter calcium homeostasis. One of the reasons for the deleterious effects of lead is its ability to strongly bind to sulfhydryl groups of proteins and to mimic or compete with calcium (Flora et al. 2007). It is known that lead, even at picomolar concentration, competes with calcium for binding sites on cerebellar phosphokinase C, thereby affecting neuronal signaling and neurotransmitter release (Bressler and Goldstein 1991), inhibiting calcium entry into cells (Simons 1993). Lead disrupts mitochondrial calcium homeostasis, intercellular oxidants levels, ATP production, and apoptogenic factors.

Rats in the benzo(a)pyrene (B(a)P) -treated groups have significantly impaired Morris water maze performance when compared to controls (Chengzhi et al. 2011). The B(a)P-induced neuronal damage was found in the hippocampus under transmission electron microscopy. Their results demonstrated that LM deficits associated protein expression signatures could be identified from tissue proteomes, as well as potential biomarkers such as retinoic acid receptor b (RARb), synaptotagmin iosfomers 1 (Syt1) and brain-derived neurotrophic factor (BDNF). This finding is the first time that multiple novel proteins that are dysregulated by B(a)P, which both enhance our understanding of B(a)P induced locomotor deficits and represent targets of novel therapeutics. Prenatal morphine can alter the synaptic complex of postsynaptic density 95 with N-methyl-D-aspartate receptor subunit in hippocampal CA1 subregion of rat offspring leading to long-term cognitive deficits (Lin et al. 2009). This morphine model might be useful for understanding mechanisms of long-term cognitive deficit induced by other ECSs such as lead and PCBs.

Originally, organophosphate pesticides (OPs) have been thought to exert their effects on brain development secondarily by their ability to inhibit cholinesterase. However, it became now clear that these agents act as developmental neurotoxicants through a number of differential mechanisms. Some of which operate at exposures below the threshold for cholinesterase inhibition may differ in their effects on brain development and their consequent impacts on behavioral performance (Paul et al. 1994; Cohn and MacPhail 1997; Itoh et al. 1997a, 1997b; Palumbo et al. 2001; Castillo et al. 2002; Levin et al. 2002; Aldridge et al. 2005; Spowart-Manning and van der Staay 2005; Timofeeva, 2008; Verma et al. 2009; Levin et al. 2010). A series of studies with toxico-dynamically equivalent exposures in neonatal rats showed that chlorpyrifos, diazinon and parathion (PRT) elicit behavioral abnormalities in association with adverse effects on acetylcholine (ACh) and serotonin (5HT) circuits, but that the underlying defects and behavioral outcomes differ among the three OPs. In particular, PRT exposure did not elicit the cognitive impairment noted with the other two OPs, as evaluated in the radial-arm maze in adolescence and young adulthood, although, it did share adverse effects on indices of ACh synaptic function.

Chemicals	Animal Species	Models and experimental types	References
Arsenic	mice	Behavioral analysis	Miyagawa et al. 2007
Arsenic	mice	Mechanistic study	Martinez-Finley et al. 2009
Arsenic	rats	Developmental exposure and behavioral analysis	Rodriguez et al. 2002
Arsenic	rats	Mechanistic study	Rodriguez et al. 2001
Aluminium-maltolate complex	mice	Mechanistic study	Kaneko et al. 2006
Aluminum	rats	Mechanistic study	Sethi et al. 2009
Aluminum	rats	Aluminum-induced memory deficit model rats	Gong et al. 2006
Copper	mice	Behavioral analysis in Alzheimer's disease models	Grossi et al. 2009

Chemicals	Animal Species	Models and experimental types	References
Copper	mice	Indicator in the Alzheimer's disease model	Fisher et al. 1991; Quinn et al. 2010
Copper	mice	Mechanistic study	Lu et al. 2006; Lu et al. 2009
Copper	hamster	Mechanistic study	Bareggi et al. 2009
Copper	rats	Mechanistic study	Obernier et al. 2002; Begum et al. 2008
Copper	rats	Competition with zinc	Railey et al. 2010
Copper	rabbit	Mechanistic study	Sparks and Schreurs 2003
Copper	rabbit	Indicator in the Alzheimer's disease model	Woodruff-Pak et al. 2007
Cobalt	rats	Mechanistic study	Nerobkova and Voronina 1988
Lead	mice	Mechanistic study	Gao et al. 2005; Railey et al. 2011
Lead	mice	Developmental exposure and behavioral analysis	Garavan et al. 2000
Lead	rats	Mechanistic study	Alkondon et al. 1990; Adhami et al. 2000 Zhang et al. 2002; Garcia-Arenas et al. 2004; Vazquez and Pena de Ortiz 2004; Haider et al. 2005; Flora et al. 2007
Lead	rats	Developmental exposure and behavioral analysis	Kumar and Desiraju 1992; Altmann et al. 1993; Yang et al. 2003
Lead	rats	Behavioral analysis	Tang et al. 1994; Fan et al. 2009
Mercury	mice	Prenatal exposure and Behavioral analysis	Montgomery et al. 2008
Mercury	mice	Developmental exposure and behavioral analysis	Yoshida et al. 2005; Eddins et al. 2008
Mercury	rats	Mechanistic study	Vicente et al. 2004
Mercury	rats	Developmental exposure and behavioral analysis	Sakamoto et al. 2002; Falluel-Morel et al. 2007
Mercury	rats	Dose-dependent study of Developmental exposure	Sakamoto et al. 2004
Mercury	monkey	Developmental exposure and behavioral analysis	Hellberg 1972
Uranium	rats	Behavioral analysis	Albina et al. 2005; Houpert et al. 2007
Uranium	rats	Developmental exposure and behavioral analysis	Sanchez et al. 2006
Vanadium	mice	Mechanistic study	Han et al. 2008
Vanadium	mice	Behavioral analysis	Avila-Costa et al. 2006
Vanadium	rats	Mechanistic study	Mao et al. 2008
Carbon monoxide	mice	Behavioral analysis	Meunier et al. 2006

Chemicals	Animal Species	Models and experimental types	References
Carbon monoxide	rats	Mechanistic study	Thom et al. 2004
Carbon monoxide	rats	Mechanistic study and Behavioral analysis	Han et al. 2007; Wang et al. 2009a
Nitrogen oxide	mice	Mechanistic study and Behavioral analysis	Reddy and Kulkarni 1998; Palumbo et al. 2007
Nitrogen oxide	rats	Mechanistic study and Behavioral analysis	Jevtovic-Todorovic et al. 2003; Kumar and Kumar 2009; Comin et al. 2010
Nitrogen oxide	rats	Behavioral analysis	Paul et al. 2003
NNAL(4-methylnitrosamino)-1-(3-pyridyl)-1-butanol)	hamster	Use of precision-cut tissue s Behavioral analysis	Richter et al. 2000
Ozone	rats	Mechanistic study and Behavioral analysis	Guerrero et al. 1999
Smoking	mice	Behavioral analysis	Paz et al. 2007
Smoking	rats	Mechanistic study	Liang et al. 2006
Smoking	rats	Developmental exposure and behavioral analysis	Levin et al. 1996
Pesticide	mice	Gufosinate-ammonium	Calas et al. 2008
Pesticide	mice	Organophosphates	Billauer-Haimovitch et al. 2009; Post et al. 2011
Pesticide	mice	quaternary ammonium herbicide	Chen et al. 2010
Pesticide	rats	Aconitine Mechanistic study	Curzon et al. 2006
Pyrethroid	rats	Pyrethroid behavioral analysis	Sinha et al. 2006
Pesticide	rats	Organophosphates	Cohn and MacPhail 1997; Paul et al. 1994 Itoh et al. 1997a; Itoh et al. 1997b; Palumbo et al. 2001; Castillo et al. 2002; Levin et al. 2002; Aldridge et al. 2005; Spowart-Manning and van der Staay 2005; Timofeeva, 2008; Verma et al. 2009; Levin et al. 2010
Pesticide	rats	Clozapine	Levin et al. 2009
Pesticide	rats	Vinclozolin fungicide	Andre, 2006
Pesticide	rats	DEET	Abdel-Rahman, 2004
Dioxin	mice	Mechanistic study	Akahoshi, 2009

Chemicals	Animal Species	Models and experimental types	References
Dioxin	rats	Mechanistic study	Marcus, 2005
Formaldehyde	mice	Mechanistic study	Tong et al. 2011
Formaldehyde	rats	Mechanistic study	Aslan, 2006; Liu, 2010
Hexachloro-Benzene	rats	Behavioral analysis	Valkusz, 2011
PCB	rats	Developmental exposure and behavioral analysis	Piedrafita, 2008; Boix, 2010 ; Jolous-Jamshidi et al. 2010
PCB	fishes	Behavioral analysis	Schantz, 2001
PFOS	mice	Developmental exposure and behavioral analysis	Johansson et al. 2008
Polycyclic aromatic hydrocarbon	mice	ADHD model	Fredriksson and Archer 2004
Polycyclic aromatic hydrocarbon	mice	Behavioral analysis Down syndrome model	Rueda et al. 2008
Polycyclic aromatic hydrocarbon	rats	ADHD model	Chengzhi et al. 2011; Lin et al. 2009; Nishio et al. 2001
Polycyclic aromatic hydrocarbon	rats	Behavioral analysis	Sun, 2005; Fedotova and Ordyan 2010
Polycyclic aromatic hydrocarbon	rats	Developmental exposure and behavioral analysis	Benetti, 2009
Polycyclic aromatic hydrocarbon	rats	Adult behavioral analysis	Revest, 2009
Trimethyltin	mice	Mechanistic study	Dey et al. 1997; Maurice et al. 1999; Kassed, 2002 ; Kim, 2007
Trimethyltin	rats	Behavioral analysis	Cohn and MacPhail 1996
Trimethyltin	rats	Mechanistic study	Oconnell et al. 1994; OConnell et al. 1996 Tsutsumi, 2002
Bisphenol	mice	Developmental exposure and behavioral analysis	Miyagawa et al. 2007
Bisphenol	rats	Mechanistic study	Poimenova et al. 2010
Paraben	rats	Developmental exposure and behavioral analysis	Kawaguchi et al. 2009
Salicylate	rats	Developmental exposure and behavioral analysis	Butcher et al. 1972

Table 3. Literature lists for effects of environmental chemicals on memory and cognition in experimental animal models.

3. Conclusion

ECSs are distributed widely and in increasing amounts over the world in the last few decades. ECSs exposure could occur through breastfeeding and hand-to-mouth activities in small children. In this review, epidemiological studies of children between ECSs exposure and neurodevelopmental disorders and experimental animal studies were focused. In our literature review, lead, methylmercury, pesticides, tobacco (cotinine), persistent organic pollutants such as PCBs, and environmental hormones such as bisphenol A and phthalates have been indicated association between neuronal disability and exposure levels in children. Children's brain and nervous system are vulnerable to adverse impacts from pollutants because they go through a long developmental process beginning shortly after conception and continuing through adolescence. This complex developmental process requires the precise coordination of cell growth and movement, and may be disrupted by even short-term exposures to environmental contaminants if they occur at critical periods of development. This disruption can lead to neurodevelopmental deficits that may have an effect on the children's achievements and behaviors even though they do not result in a diagnosable disorder.

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Learning Disabilities

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Learning disability is a classification that includes several disorders in which a person has difficulty learning in a typical manner. Depending on the type and severity of the disability, interventions may be used to help the individual learn strategies that will foster future success. Some interventions can be quite simplistic, while others are intricate and complex. This book deserves a wide audience; it will be beneficial not only for teachers and parents struggling with attachment or behavior issues, but it will also benefit health care professionals and therapists working directly with special needs such as sensory integration dysfunction.

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