Scientific Educational Journal "educ@tional circle"
Volume 8, Issue 3, 2020 © educ@tional circle ISSN: 2241-4576

Effect of chemical contaminants on brain development and mental health of preschool and school-age children: a review

Maria Lyssikatou, *Secondary School Chemistry teacher, mlyss@gmx.net*

Andreas Oikonomou, *Associate Professor of ASPETE, Department of Pedagogy, School of Pedagogical and Technological Education (ASPETE), Papanastasiou 13, 54639, Thessaloniki, Greece, aoikonomou@aspete.gr*

Abstract: Chemical contamination refers to the presence of chemicals in places where they should not be found, including the workplace, home, food and environment. It can also refer to chemicalsthat are present at higher concentrations than usual or at concentrations that are considered to be hazardous to human health.The aim of the present study is to review recent research related to the effects of the main inorganic and organic chemical contaminants on brain development and mental health of preschool and school-age children.In addition, possible ways of preventing and reducing chemical contamination in schools are suggested. The results of recent findings showed that the exposure of children to chemical contaminants was associated with structural changes in the developing human brain in regions that affect working memory, attention and executive function. Intelligent quotient deficits,motor and learning problems,autism spectrum and attention deficit hyperactivity disorders were observed in children exposed to various chemical contaminants. Furthermore, other studies showed that toxic environmental exposure was related to the appearance of antisocial and violent behaviour as well as other psychological issues.Therefore, it can be concluded that chemical contaminants may affect the cognitive function and the mental health of preschool and school-age children.

Keywords: chemical contaminants; neurotoxic substances; brain development; mental health, cognitive development, preschool and school-age children

Introduction

Chemical contamination refers to the presence of chemicals in places where they should not be normally found, including the workplace, home, food and the environment. It may also refer to chemicals present at higher concentrations than usual or at concentrations that are considered to be hazardous to human health.

Chemical contamination is one of the most important problems in developed countries as well as in developing countries. Several chemical contaminants have been classified as known neurotoxic substances and it is estimated that there are thousands of potential neurotoxic substances that have not been yet studied. These substances are associated with mental health and developmental disorders of the brain. As children are more vulnerable to chemical contamination, there is an increased risk of developing neuropsychological disorders.

Children have a higher degree of exposure to toxic chemicals compared to adults since they have a higher metabolic rate and consequently higher consumption of food, water and air per kilogram of body weight. Also, the metabolism of children is immature making them less capable of breaking down and eliminating toxic substances than adults (Rauh & Margolis, 2016).Not to mention that children have longer life spans to develop chronic diseases than adults. Additionally, the behavior of children is different from that of adults, which leads to different routes of exposure. For example, children play usually on the ground where they can be exposed to various chemicals that exist on the ground, on the floor and in the dust. Their tendency to place various objects or toys in their mouth and to touch dangerous chemicals increases their exposure and poses a direct threat to their health and safety. Moreover, children are often unable to read warning labels on products and as a result they are at higher risk than adults (European Commission, 2017).

The adverse effects of children's exposure to chemical contaminants are related to the entire neurodevelopmental spectrum including mental disorders, motor and learning disabilities, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) as well as subtler disorders such as slightly reduced Intelligent Quotient (IQ) or attention problems. Furthermore, it has been found that the manifestation of antisocial and violent behavior in school-age children is often related to their exposure to certain neurotoxic chemicals in their early stages of development (Liu et al., 2014; Gump et al., 2017; Furlongetal., 2014).

1. Types of chemical contaminants

There are two types of chemical contaminants:

- Inorganic chemical contaminants, such as heavy metals (e.g. lead (Pb), mercury (Hg), manganese (Mn), arsenic (As), nickel (Ni), copper (Cu) thallium (Tl), cadmium (Cd)), nitrate and nitrite ions ($NO_3^-$and NO_2^- respectively), ozone (O_3), nitrogen oxides (NO_x), carbon monoxide (CO), carbon dioxide (CO_2), sulfur dioxide (SO_2) and others.
- Organic chemical contaminants, such as organic solvents, hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), bisphenol A (BPA) and other phenols, pesticides, polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polybrominated diphenyl ethers (PBDEs), perfluoroalkyl substances (PFASs) and phthalates.

Many of the above organic contaminants are characterized as persistent organic pollutants (POPs). These compounds were banned decades ago, but they can still be detected in the environment at relatively high concentrations due to their previous high production volume and long half-time. Half-time is defined as the time required for the reduction of the chemical contaminant concentration to the half.

Some of the above inorganic contaminants (e.g. various oxides) and organic (e.g. organic solvents and hydrocarbons) constitute the atmospheric contaminants. Particulate matter (PM) is a general term used to classify atmospheric contaminants and refers to the sum of solid and liquid particles suspended in the air. These particles result from anthropogenic activities as well as natural sources. Industrial facilities, power stations, vehicles, incinerators, dust and fires are the main sources of PM (Morabet,2018).

2. Inorganic chemical contaminants (Heavy metals)

The potential damage of children's exposure to heavy metals has been the focus of research for many years. The adverse effects of increased lead (Pb) concentration have been extensively studied in the area of cognitive function. Although there is no known level of lead exposure that is considered to be safe for children, the US Centers for Disease Control and Prevention (CDC) has seta reference value of 5 μg/dL for blood Pb level.

Cognitive deficits associated with lead exposure are considered to be irreversible (Mazumdar et al., 2011). The effects of various metals such as Pb, arsenic (As), chromium (Cr), manganese (Mn) and iron (Fe) on the cognitive function of children aged 6-12 years were studied in Brazil (Nascimento at al., 2015).The Raven's Colored Progressive Matrices (RCPM) test was used for the assessment of the cognitive ability. A decreased IQ was observed for children of rural areas compared to urban areas, whereas cognitive deficits were mainly related to children's exposure to Mn and Fe. These resultsindicate the importance of monitoring the concentration of metals that are considered to be essential, especially iron, as they can cause adverse effects in children when they exceed normal levels.

Cadmium (Cd) is also considered to be a toxic metal. One study investigated the relationship between the exposure to Cd and the neuropsychological development in 6-9-year-old children (Rodríguez-Barrancoetal.,2014). The neuropsychological development was assessed with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and with three automated tests from the Behavioral Assessment and Research System (BARS): Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT). It was observed that doubling the urinary cadmium levels was associated with a two-point decrease in IQ in boys. The results of this study indicate the neurotoxic effect of postnatal exposure to low Cd levels in children. Concurrently, these results advocate the assumption that there are differences between sexes regarding the neurotoxic effects in children.

Methylmercury (CH_3Hg or MeHg) is one of the most toxic forms of mercury and is found in certain seafood, which is also a major source of nutrition for certain populations such as the Inuit. Initially, a study of the behavioral function of 110 Canadian Inuit children aged 5 years was conducted (Plusquellecetal., 2010). A modified version of the Bayley Scales for Infant Development II was used to assess children's behavior. The findings of the study showed that childhood exposure to Pb was associated with increased impulsivity, irritability and inattention. Subsequently, during monitoring of the same population, high levels of MeHgand

Pb were measured in children aged 11 years in average that presented a decreased IQ (Jacobsonetal., 2015). Furthermore, a correlation between high levels of Hg and Pb with a higher incidence of behavior that is consistent with ADHD was reported (Boucheretal., 2012). ADHD is a brain disorder and is characterized by a variety of impairments including difficulty of the child to maintain attention or to focus on a particular task as well as impulsivity, hyperactivity, lethargic behavior or a combination. Furthermore, it was observed that postnatal exposure of the same population of Canadian Inuit children to chemical contaminants mainly affectedtheir fine motor skills indicating that children remain vulnerable to toxic contaminants for years after birth (Boucheretal., 2016).

Postnatal exposure of children aged 5-12 years to Pb may be associated with a higher risk of clinically diagnosed ADHD even at low levels (Kim et al., 2013). Another ADHD-related study was carried out on 240 children aged 3-7 years living in Guiyu, an internationally known e-waste recycling town in China (Liu et al., 2014).The main finding of the study was that the exposure to heavy metals was related tobehavioral problems, including ADHD as well as antisocial behavior.

ASD is a neurodevelopmental disorder that is constantly increasing nowadays. Environmental factors associated with ASD usually appear as combinations of multiple chemical contaminants making it difficult to discern the effect of a particular contaminant (Rauh & Margolis, 2016). In a study of children with ASD the autism group showed higher levels of several toxic metals including Pb in red blood cells (41%) and urine (74%) compared to the control group (Adams et al., 2013).

The association between exposure to Pb and Hg and behavioral and psychological problems such as hostility, destructive behavior, emotion regulation and autistic behavior has recently been studied (Gump et al., 2017).Children exhibited higher levels of hostility as well as anti-inflammatory and provocative behavior with increasing levels of Pb. In addition, children appeared more unhappy and uncertain about their emotions and they displayed communication problems. These significant correlations were found inblood Pb levels ranging from 0.19 to 3.25 μg/dL, i.e. lower than the reference value of 5 μg/dL. This was the first study to show a correlation between very low levels of Pb exposure and psychological mechanisms of fundamental importance that could elucidate more convoluted issues such as delinquency.

The majority of the studies concerning the adverse effects of As have been conducted in the developing countries where water is pumped from wells. In Bangladesh, a linear decrease of 1-3 points in verbal IQ test as well as in full scale IQ test score was reported for every 100 μg/L increase in urine Asin girls, but not boys, aged 5 years (Hamadanietal., 2011).Additional evidence comes from another study in the same area in children aged 8-11 years (Wassermanetal., 2011). The results of this study showed than an increase of one unit (1μg/L) in the level of blood As was associated with a statistically significant decrease of 1.49 points in verbal IQ test and decreases in full scale IQ test score, in working memory, perceptual reasoning and processing speed. Furthermore, blood As levels in 304 children aged 8-11 years were negatively associated with motor function, body coordination and fine motor control (Parvezetal., 2011). A lower performance of children in cognitive tests was also observed. Conversely, a reduction in As concentration was associated withan improvement of working memory in 10-year-old children (Wassermanet al., 2016).

3. Organic chemical contaminants

3.1. Pesticides

Organophosphates are organic synthetic phosphorus compounds which are widely used in agriculture. Organophosphate pesticides are considered to be neurotoxic at high doses. The primary role of organophosphates at these doses is the inhibition of acetylcholinesterase, which leads to the accumulation of acetylcholine between nerves and muscles (neuromuscular synapses). The exposure to these pesticides is measured by the presence of dialkyl phosphate (DAP) metabolites (Eskenazietal., 2014). The chemical structure of DAP is illustrated in Fig. 1. The two main factors that are likely to influence the sensitivity to the adverse effects of these pesticides are genes and age at the time of exposure. The enzyme paraoxonase 1 (PON1) plays a significant role in the detoxification and removal of several oxon derivatives of these pesticides, preventing thus the inhibition of acetylcholinesterase (Eskenazietal., 2014). Specifically, individuals with a particular PON1 genotype appear to be less susceptible to the effects of organophosphate pesticides (Huenetal., 2010).

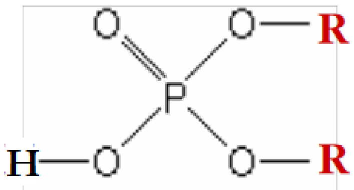

Figure1.Chemical structure of dialkyl phosphate (R=alkyl group)

Exposure to organophosphate pesticides has adverse effects on children's cognitive function and behavior (Furlong et al., 2014).It was found that exposure of 7-year-old children to organophosphate pesticides, as measured by DAP metabolite levels, was negatively related to cognitive ability (IQ) and attention(Bouchardetal., 2011).In addition, children aged 6-11 years who had been postnatally exposed to organophosphate pesticides showed reduced IQ, verbal comprehension and processing speed scores(González-Alzagaetal., 2015).These effects were more noticeable in boys compared to girls.Another study examined the effect of PON modification on neurodevelopment upon exposure to organophosphate pesticides (Engeletal., 2011).According to the results of this study, increased levels of DAP metabolites in children aged 6-9 years were associated with decreased full-scaleIQ test score and perceptual reasoning. However, this effect was observed only in children whose mothers had a specific genotype of the enzyme PON1. Additional evidence comes from a study of 5- and 7-year-old children (Eskenazietal., 2014).The above studies indicate that the PON1 genotype and levels may be directly related to the neurodevelopment and the academic performance of school-age children when exposed to organophopshate pesticides.

As mentioned above, exposure to organophosphate pesticides can adversely affect children's behavior. Prenatal exposure of 5-year-old Latino children was related to ADHD-like behavior (Marksetal., 2010).Another study investigated the relationship between prenatal exposure to organophosphate pesticides and antisocial behavior in childhood, as measured by the social responsiveness scale (SRS)(Furlongetal., 2014). The results demonstrated that prenatal exposure of 7-9-year-old children to organophosphate pesticides was associated with lower scores in SRS. These differences were most prominent in black boys, perhaps due to the different sources of exposures of the two races as well as the increased environmental sensitivity of the boys.

Chlorpyrifos (O,O-diethyl-O-(3,5,6-trichloro-2-pyridyl)phosphorothioate) is awidely usedorganophosphate insecticide (Fig. 2). The prenatal exposure of children aged 11 years in average to this specific insecticide caused hand tremor, indicating the effect of the insecticide on the central nervous system function (Rauhetal., 2015).

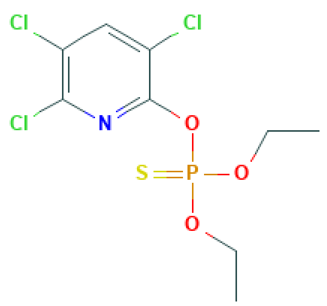

Figure 2. Chemical structure of chlorpyrifos

Chloropicrin, metam sodium, 1,3 dichloropropene (Fig. 3) and methyl bromide (CH_3Br) are common fungicides mainly used to reduce soil pathogens and pests before the planting of crops.

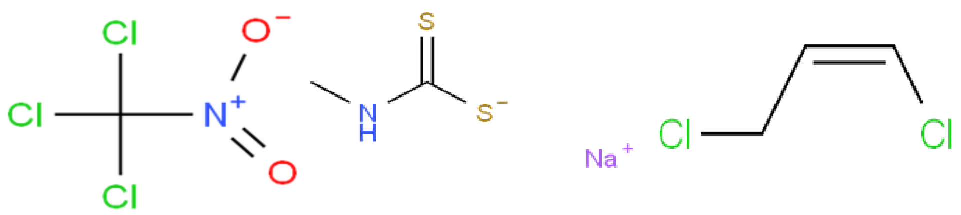

Figure 3. Chemical structures of chloropicrin, metam sodium and 1,3 dichloropropene respectively

The relationship between home proximity to the use of the above fungicides and the neurodevelopment of 7-year-old children was investigated(Gunieretal., 2017a). The use of fungicides was estimated within 3, 5 and 8 km from the families' homes during pregnancy and up to 7 years after birth. Reductions of 2.6 and 2.4 in the full-scale IQ test score were recorded for each 10-fold increase in the use of methyl bromide and chloropicrin within 8 km from the children's homes respectively. A previous study of the same group indicated associations between children's IQ test scores and prenatal use of organophosphate insecticides within 1 km from the family' s homes during pregnancy (Gunier et al.,2017b). Similar results were reported in the same study with other potentially neurotoxic pesticides such as carbamates, neonicotinoids, pyrethroids and maneb. Furthermore, children were at higher risk of developing ASD with use of organophosphate pesticides within 1.5 km from their home during the prenatal period (Sheltonetal., 2014).

3.2. Polychlorinated biphenyls (PCBs) - polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)

Polychlorinated biphenyls (PCBs) (Fig.4)are a group of aromatic chlorinated hydrocarbons comprising over 200 members. PCBs are stable compounds that are highly resistant to breakdown processes. Their industrial applications were several such as e.g. in hydraulic fluids, inks, lubricants and heat transfer fluids. The production and use of PCBs was banned in the early 1980s due to their toxicity. However, they can still be detected in the environment as they are considered to be POPs.

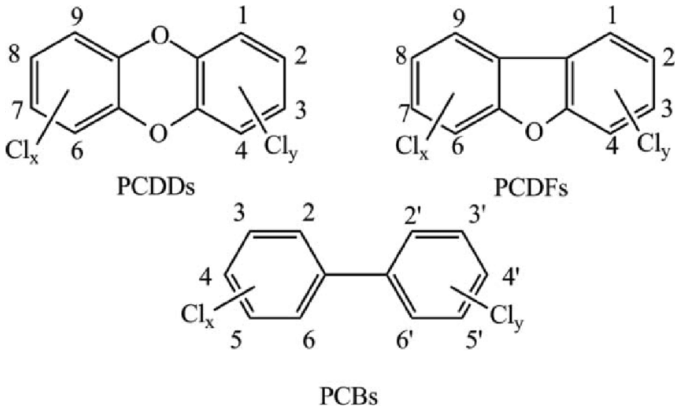

Figure 4. Chemical structures of PCDDs, PCDFs and PCBs (x,y=1-4)

The term "dioxins" covers a group of 75 chemically similar polychlorinated dibenzo-p-dioxins (PCDDs) and 135 polychlorinated dibenzofurans (PCDFs) (Fig. 4). Dioxins are formed during combustion processes and as by-products of industrial processes. They are highly resistant to biodegradation processes and are considered to be highly toxic to humans.

The reaction time of 8-9-year-old children from Slovakia after their exposure to PCBs was investigated(Šovčíkováetal., 2015). The results showed that exposure of children to PCBs was associated with prolonged reaction time, suggesting impaired cognitive functions.Postnatal exposure of Canadian Inuit children aged 11 years in average to PCBs caused a fine motor delay(Boucheretal., 2016). This study reinforces the view that chronic exposure to seafood chemical contaminants affects fine motor skills (Boucheretal., 2016). Prenatal exposure of 7-11-year-old children to PCBs was also related to ADHD-like behavior (Sagivetal., 2010). The

Conners' Rating Scale for teachers (CRS-T) was used for the evaluation. According to the results, a higher risk of ADHD-like behavior wasobserved in children with higher PCBs levels. The impact of exposure of children aged 8.5 and 9.5 in average to PCBs, PCDDs and PCDFs on attention-related performance and behavior was examined in Germany (Neugebaueretal., 2015). An increase in prenatal concentrations of the above chemicals was significantly associated with an increase of omission errors of 42% for PCBs and 47% for PCDDs and PCDFs.This was the first study to examine the impact of PCBs, PCDDs and PCDFs on the attention performance of school-age children and the results showed a possible link between prenatal exposure of children to the above chemical contaminants and ADHD.

One of the herbicides sprayed in Vietnam during US military operations between 1961 and 1971 was Agent Orange which contained 2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD). This dioxin is considered to be the most toxic of the PCDDs group. The effect of postnatal dioxin exposure of 5 year-old children on the neurodevelopment including motor coordination and cognitive function was investigated in dioxin-contaminated areas of Vietnam (Tranetal., 2016).The results indicated a significant effect of dioxins on the neurodevelopment of children, especially in boys. In addition, it was found that high exposure to PCDDs and PCDFs in combination with high exposure to TCDD may increase autistic traits associated with developmental coordination disorder, especially in boys. The findings of this study suggest that boys are more vulnerable to dioxin toxicity than girls. It seems that maternal exposure to dioxins may affect the fetal testosterone levels which play a major role in autistic traits during childhood (Tranetal., 2016).

3.3.Polybrominated diphenylethers (PBDEs)

Polybrominated diphenyl ethers (PBDEs) (Fig. 5) are a group of organic compounds used as flame retardants with a wide range of applications. PBDEs are POPs with lipophilic properties that accumulate in adipose tissues and exhibit toxicity.

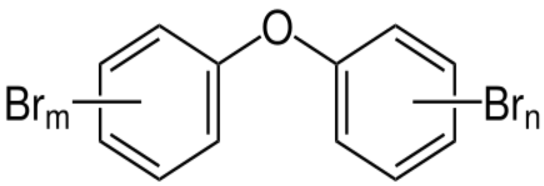

Figure 5. Chemical structure of PBDEs (m,n=1-5)

In a US study, exposure of5- and 7-year-old children to PBDEs was associated with ADHD and reduced fine motor coordination (Eskenazietal., 2013).Furthermore, in 7-year-olds attention problems and decreases in processing speed, perceptual reasoning, verbal and full-scale IQ were reported. Similarly, prenatal concentrations of PBDEs were found to be negatively correlated with reading ability and full-scale IQ and positively correlated to externalizing behavioral problems in 8-year-old children (Zhangetal., 2017).Prenatal exposure of 5-year-old children to PBDEs was also associated with lower IQ and a higher level of hyperactivity (Chenetal., 2014). Similar results were observed in 8-year-old children (Vuongetal., 2017). Postnatal exposure of these children was found to be associated with lower full-scale IQ, increased hyperactivity and aggressive behavior.Prenatal exposure of children aged 3-7 years to PBDEs was related to attention problems as well (Cowelletal., 2015). This was the first study to address the impact of PBDEs involving preschool and school-age children.

Executive function plays a critical role in the child's behavior and is rarely studied in relation to potential neurotoxic substances. Recently, it was reported that prenatal exposure of children aged 5 and 8 years to PBDEs may be associated with reduced executive function (Vuongetal., 2016).

3.4. Bisphenol A (BPA)

Bisphenol A (BPA) (Fig. 6) is widely used in the manufacture of plastics and epoxy resins. BPA is a well-knowncomponent of durable polycarbonate plastics used in a variety of everyday objects such as CDs, DVDs, computers, etc. BPA is considered to have toxic impact on human health.

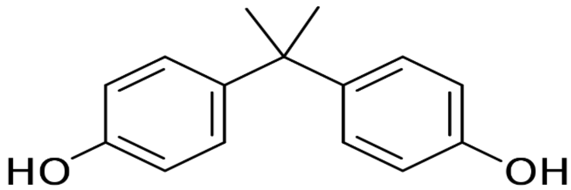

Figure 6. Chemical structure of BPA

The exposure of children aged 7 and 9 years to BPA was found to be related to behavioral problems including anxiety, depression and hyperactivity, mainly in boys (Harleyetal., 2013). Similar results were reported in another study of the effects of BPA exposure in children aged 7-9 years (Roenetal., 2015)as well as in children aged 10-12 years (Pereraetal., 2016). The prenatal exposure of children to BPA was associated with more anxiety and depression symptoms, mainly in boys.Furthermore, exposure of children aged 9-11 years to BPA influenced their behavior, as children with elevated BPA concentrations had more physical complaints, thinking problems and greater social problems (Perez-Lobatoetal., 2016). It was also reported that children's exposure to BPA was related to ADHD, with effects being more prominent in boys than girls (Tewaretal., 2016).

The results of the above studies indicate that exposure to BPA may affect children's behavior differently depending on gender and exposure time. The different effects observed in the behavior of boys and girls may be due to estrogenic effects or other sex hormone disruption mechanisms resulting from the exposure of the child's thyroid parameters to BPA (Ghassabian&Trasande, 2018).

3.5. Perfluoroalkyl substances (PFASs)

Perfluoroalkyl substances (PFASs) are a group of chemical compounds widely used as water and fat repellents, in clothing, in detergents, in materials that come in contact with foods, in cosmetics and in other consumer products (Lau 2012). PFASs are neurotoxic compounds. Perfluorooctane sulfonic acid (PFOS) (Fig. 7) is the most known compound of the group.

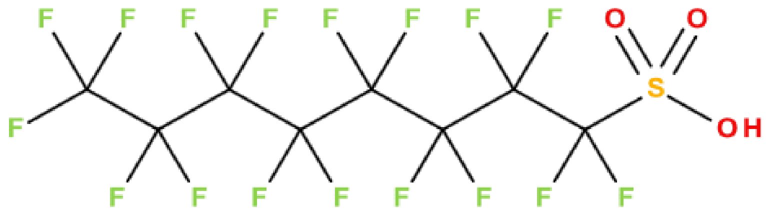

Figure 7. Chemical structure of PFOS

Prenatal exposure of children aged 5-9 years to PFASs had moderate effect on the neurodevelopment with regard to the manifestation of hyperactive behavior (Høyeretal., 2015). In another study in Asia, it was reported that prenatal exposure of 7-year-old children to PFASs was related to ADHD (Lien et al., 2016). High prenatal PFASs concentrations were associated with behavioral problems in Danish children aged 5 and 7 years (Oulhote et al., 2016).Furthermore, prenatal exposure of children 5 and 8 years to PFASs may be related to reduced executive function (Vuongetal., 2016).

3.6. Phthalates

Phthalates (Fig. 8) are a group of chemical compounds widely used as plasticizers. The latter ones aresubstances added to plastics to increase their flexibility. Phthalates are employed in a variety of commercial products such as children's toys, food packaging, medical equipment,furniture and cosmetics.

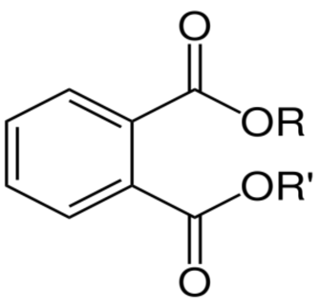

Figure 8. Chemical structure of phthalates (R and R' are general substituents)

A study in Taiwan showed that prenatal exposure of 8-year-old children to phthalates was associated to externalizing problems, such as delinquent and aggressive behaviours (Lienetal., 2015). Another study also conductedin Taiwan showed that higher postnatal levels of phthalates were associated with lower IQ scores in children aged 2-12 years (Huangetal., 2015). These results indicate that continuous exposure to phthalates can adversely affect children's cognitive development.

3.7. Atmospheric contaminants

Air pollution is a major environmental problem worldwide and a suspected neurotoxicant. It has been proven that high exposure of school-age children to atmospheric contaminants is associated with slower brain maturation and it adversely affects brain function (Pujoletal., 2016).

In Spain, children aged 7-10 years attendingschools built on highly contaminated areas exhibited lower cognitive development than the ones attending schoolsbuilt on low contaminated areas (Sunyeretal., 2015). Atmospheric contamination at school was also associated with fluctuations in attention (Sunyeretal., 2017). In addition, exposure of school-age children to fine particulate matter (PM) with a diameter of 2.5 μm or less ($PM_{2.5}$) and elemental carbon (EC) during walking to school was negatively associated with working memory (Alvarez-Pedrerol et al., 2017). It was reported that exposure of school-age children to traffic-related air pollutants adversely affected children's cognitive development (Fornsetal., 2016).The children were monitored for one year and it appeared thatworking memory and attentionin particular were adversely affected. Finally, the same team monitored the levels of traffic-related air pollutants in relation to children's academic performance over a period of 3.5 years (Fornsetal., 2017). The results showed a continuous negative correlation between the levels of traffic-related air pollutants and the children's cognitive development indicating how harmful atmospheric contamination in schools is.

4. Prevention and reduction of chemical contamination in schools

In general, the air qualityin schools plays an important role in the development of the children's brains. Specific measures should be taken by governments, teachers and parentsin order to prevent and reduce chemical contamination in schools. Initially, awareness should be raised within as well as outside the school community about the impact of chemical contamination on children's health and on public health overall. In the context of this awareness, workshops on chemical contamination could be organized by school principals, teachers and the Parents and Guardians Association. Various specialists (e.g. medical practitioners, chemists) should be involved in these workshops to inform teachers, parents and students about the perils associated with toxic contaminants. Furthermore, they should inform the school community about possible ways to prevent and reduce chemical contamination in schools and at home.

The state should take measures to reduce traffic on the roads surrounding the schools and promote the use of public transport to school. It should also create a greener environment through plantation of trees and plants in the schoolyards.A regular replacement of the sand in school playgrounds is also crucial in order to reduce the accumulation of chemical contaminants and other pathogenic microorganisms (Rivas et al., 2018). In addition, another important measure would be to enhance students’ environmental education and information on the recycling of materials and also on the management of chemicals in the school environment. For this reason, recycling bins should be placed in every schoolyard. In addition, many commercially available toys have been found to be toxic (Becker et al., 2010). It is the state's duty to remove any toxic toys from the school premises and to inform the parents. Another high priority of the local regulatory authorities is the surveillance of the drinking water quality and the maintenance of the pipes in schools as well as the monitoring of the quality of food and drinks served by the school canteens.

As already mentioned,exposure of school-age children to traffic-related air pollutants has been shown to depend onwalking distance to school (Alvarez-Pedrerol et al., 2017). Therefore, future schools should be preferably be built away from busy streets. Regular ventilation should take place to improve the air quality in the classrooms. In areas of high atmospheric contamination, a ventilation system with filtered air may be used in the classrooms, whereas in areas of high ozone concentrations, if mechanical ventilation is used, it is highly recommended that ozone traps are installed in the system (Rivas et al., 2018). Furthermore, the classrooms and the entire school area should be cleaned after school hours andthe cleaning staff is advised to use environmentally friendly cleaning products. Finally, construction materials, paints and furniture used for the construction or for the renovation of school buildings should be carefully selected in order to avoid high exposure of children to volatile organic compounds (Rivas et al., 2018).

Perhaps, all of the above ways of preventing and reducing chemical contamination in schools may not be enough to solve such a serious problem. Nevertheless, they constitute a good starting point to ensure that the children's quality of life is improved.

5. Conclusions

Chemical contamination is considered to be one of the most important problems worldwide. At global level, children are exposed daily to numerous chemical contaminants, many of which are neurotoxic substances that adversely affect their brain development and mental health. The objective of this review was to identify and access recent scientific literature related to the effects of the main inorganic and organic chemical contaminants on brain development and mental health of preschool and school-age children. The results reported by the studies covered in this review showed that the exposure of preschool and school-age children to chemical contaminants was associated with structural changes in the developing human brain in regions that affect working memory, attention and executive function. IQ deficits, motor and learning problems, autism spectrum and attention deficit hyperactivity disorders were observed in children exposed to various chemical contaminants. Furthermore, other studies indicated that toxic environmental exposure was associated with the manifestation of antisocial and violent behavior as well as other psychological issues. Consequently, it can be deduced that exposure of preschool and school-age children to various chemical contaminants may affect their cognitive function and mental health. However, further research is required to study the exposure of children to combinations of different chemical contaminants and to clarify the mechanisms related to other factors such as sex.

Finally, specific measures could be implementedby the state and the individuals in order to prevent and reduce chemical contamination in schools. However,most of all, it is imperative for usto realizethat every child has an inalienableright to a healthy and safe living environment.

References

Adams,J.B., Audhya,T., McDonough-Means,S., Rubin,R.A., Quig,D., Geis,E.,Gehn, E., Loresto, M., Mitchell, J., Atwood, S., Barnhouse, S.,&Lee, W.(2013). Toxicological Statusof Childrenwith Autism vs. Neurotypical Children and theAssociation with Autism Severity. *Biol Trace ElemRes 151*(2), 171–180. https://doi.org/10.1007/s12011-012-9551-1

Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M., Suades-González, E., Donaire-Gonzalez, D., Cirach,M., de Castro, M., Esnaola, M., Basagaña, X., Dadvand, P., Nieuwenhuijsen, M., &Sunyer, J. (2017).Impact of commuting exposure to traffic-related air pollution on cognitive development in children walking to school.*Environ Pollut 231*(1), 837-844. https://doi.org/10.1016/j.envpol.2017.08.075

Becker, M., Edwards, S., &Massey, R.I. (2010).Toxic Chemicals in Toys andChildren’s Products: Limitations ofCurrent Responses andRecommendations for Governmentand Industry. *Environ Sci Technol 44*(21), 7986-7991. https://doi.org/10.1021/es1009407

Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K., Vedar, M., Calderon, N.,Trujillo, C., Johnson, C., Bradman, A., Barr, D.B., &Eskenazi, B. (2011).Prenatal Exposure to Organophosphate Pesticides and IQ in 7-year-Old Children.*Environ Health Perspect 119*(8), 1189-1195. https://doi.org/10.1289/ehp.1003185

Boucher,O., Jacobson, S.W., Plusquellec, P., Dewailly, E., Ayotte, P., Forget-Dubois, N., Jacobson, J.L., &Muckle, G. (2012).Prenatal Methylmercury, Postnatal Lead Exposure, and Evidence of Attention Deficit/Hyperactivity Disorder among Inuit Children in Arctic Québec.*Environ Health Perspect 120*(10), 1456-1461.https://doi.org/10.1289/ehp.1204976

Boucher,O., Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W., &Jacobson, J.L. (2016).Altered fine motor function at school age in Inuit children exposed to PCBs, methylmercury, and lead. *Environ Int 95*,144-151. https://doi.org/10.1016/j.envint.2016.08.010

Chen, A., Yolton, K., Rauch, S., Webster, G.M., Hornung, R., Sjödin,A., Dietrich, K.N., &Lanphear, B.P. (2014).Prenatal Polybrominated Diphenyl Ether Exposures and Neurodevelopment in U.S. Children through 5 Years of Age: The HOME Study. *Environ Health Perspect 122*(8), 856-862. https://doi.org/10.1289/ehp.1307562

Cowell, W.J., Lederman, S.A., Sjödin, A., Jones,R., Wang, S., Perera, F.P., Wang, R., Rauh, V.A., &Herbstman, J.B. (2015).Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3–7 years. *NeurotoxicolTeratol 52*,143-150. https://doi.org/10.1016/j.ntt.2015.08.009

Engel, S.M., Wetmur, J., Chen, J., Zhu, C., Barr, D.B., Canfield, R.L., &Wolf, M.S. (2011). Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood. *Environ Health Perspect119*(8), 1182-1188. https://doi.org/10.1289/ehp.1003183

Eskenazi, B., Chevrier, J., Rauch, S.A., Kogut, K., Harley, K.G., Johnson, C., Trujillo, C., Sjödin, A., &Bradman, A. (2013).*In Utero* and Childhood Polybrominated Diphenyl Ether (PBDE) Exposures and Neurodevelopment in the CHAMACOS study. *Environ Health Perspect 121*(2), 257-262. https://doi.org/10.1289/ehp.1205597

Eskenazi, B., Kogut, K., Huen, K., Harley, K.G., Bouchard, M., Bradman, A., Boyd-Barr, D., Johnson, C., &Holland, N. (2014).Organophosphate pesticide exposure, PON1, and neurodevelopment in school-age children from the CHAMACOS study. *Environ Res 134*,149-157.https://doi.org/10.1016/j.envres.2014.07.001

European Commission (2017). Study for the strategy for a non-toxic environment of the 7th Environment Action Programme.https://goo.gl/vY2bUK

Forns, J., Dadvand, P., Esnaola, M., Alvarez-Pedrerol, M., López-Vicente, M., Garcia-Esteban, R.,Cirach, M., Basagaña, X., Guxens, M., &Sunyer, J. (2017).Longitudinal association between air pollution exposure at school and cognitive development in school children over a period of 3.5 years. *Environ Res 159*,416-421. https://doi.org/10.1016/j.envres.2017.08.031

Forns, J., Dadvand, P., Foraster, M., Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M.,Suades-Gonzalez, E., Garcia-Esteban, R., Esnaola, M., Cirach, M., Grellier, J., Basagaña, X., Querol, X., Guxens, M., Nieuwenhuijsen, M.J.,&Sunyer, J. (2016).Traffic-Related Air Pollution, Noise at School, and Behavioral Problems in Barcelona Schoolchildren: A Cross-Sectional Study. *Environ Health Perspect 124*,529-535. https://doi.org/10.1289/ehp.1409449

Furlong, M.A., Engel, S.M., Barr, D.B., &Wolff, M.S.(2014). Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood. *Environ Int 70*,125-131. https://doi.org/10.1016/j.envint.2014.05.011

Ghassabian, A., &Trasande, L. (2018).Disruption in Thyroid Signaling Pathway: A Mechanism for the Effect of Endocrine Disrupting Chemicals on Child Neurodevelopment. *Front Endocrinol 9*(204), 1-8. https://doi.org/10.3389/fendo.2018.00204

González-Alzaga, B., Hernández, A.F., Rodríguez-Barranco, M., Gómez, I., Aguilar-Garduño, C., López-Flores,I.,Parrón, T., &Lacasaña, M. (2015).Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain.*Environ Int 85*,229-237. https://doi.org/10.1016/j.envint.2015.09.019

Gump, B.B., Dykas, M.J., MacKenzie, J.A., Dumas, A.K., Hruska, B., Ewart, C.K., Parsons, P.J., Palmer, C.D., &Bendinskas, K.(2017). Background lead and mercury exposures: Psychological and behavioral problems in children. *Environ Res 158,*576-582. https://doi.org/10.1016/j.envres.2017.06.033

Gunier, R.B., Bradman, A., Castorina, R., Holland, N.T., Avery, D., Harley, K.G., &Eskenazi, B. (2017a).Residential proximity to agricultural fumigant use and IQ, attention and hyperactivity in 7-year old children. *Environ Res 158,*358-365. https://doi.org/10.1016/j.envres.2017.06.036

Gunier, R.B., Bradman, A., Harley, K.G., Kogut, K., &Eskenazi, B. (2017b).Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children. *Environ Health Perspect125*(5), 1-8. https://doi.org/10.1289/EHP504

Hamadani, J.D., Tofail, F., Nermell, B., Gardner, R., Shiraji, S., Bottai, M.,Arifeen, S.E., Huda, S.N.,&Vahter, M.(2011). Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. *Int J Epidemiol 40*(6), 1593-1604. https://doi.org/10.1093/ije/dyr176

Harley, K., Gunier, R.B., Kogut, K., Johnson, C., Bradman, A., Calafat, A.M., &Eskenazi, B. (2013).Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. *Environ Res 126,*43-50. https://doi.org/10.1016/j.envres.2013.06.004

Høyer, B.B., Ramlau-Hansen, C.H., Obel, C., Pedersen, H.S., Hernik, A., Ogniev,V.,Jönsson, B.A.G., Lindh,C.H., Rylander, L., Rignell-Hydbom, A., Bonde, J.P., &Toft, G. (2015).Pregnancy serum concentrations ofperfluorinated alkyl substances and offspring behaviour and motor development at age 5–9years – a prospective study. *Environ Health14*(2), 1-11. https://doi.org/10.1186/1476-069X-14-2

Huang, H.B., Chen, H.Y., Su, P.H., Huang, P.C., Sun, C.W., Wang, C.J., Chen, H.Y., Hsiung, C.A.,& Wang, S.L. (2015).Fetal and Childhood Exposure to PhthalateDiesters and Cognitive Function in ChildrenUp to 12 Years of Age: Taiwanese Maternaland Infant Cohort Study. *PLoS One 10*(6), 1-13. https://doi.org/10.1371/journal.pone.0131910

Huen, K.,Harley, K.,Bradman, A., Eskenazi, B., &Holland, N. (2010).Longitudinal changes inPON1enzymaticactivitiesinMexican–American mothersand children withdifferentgenotypesandhaplotypes.*Toxicol Appl Pharmacol244*(2), 181–189.https://doi.org/10.1016/j.taap.2009.12.031

Jacobson, J.L., Muckle, G., Ayotte, P., Dewailly,É.,&Jacobson, S.W. (2015). Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ. *Environ Health Perspect123*(8), 827-833. https://doi.org/10.1289/ehp.1408554

Kim, S., Arora, M., Fernandez, C., Landero, J., Caruso, J., &Chen, A. (2013).Lead, mercury, and cadmium exposure and attention deficit hyperactivity disorder in children. Environ Res 126:105-110. https://doi.org/10.1016/j.envres.2013.08.008

Lau,C. (2012). Perfluorolakyl acids: Recent research highlights. *ReprodToxicol 33*(4), 405-409. https://doi.org/10.1016/j.reprotox.2012.03.002

Lien, G.W., Huang, C.C., Shiu, J.S., Chen, M.H., Hsieh, W.S., Guo, Y.L., &Chen, P.C. (2016).Perfluoroalkyl substances in cord blood and attention deficit/hyperactivity disorder symptoms in seven-year-old children. *Chemosphere 156,*118-127.https://doi.org/10.1016/j.chemosphere.2016.04.102

Lien,Y.J., Ku, H.Y., Su, P.H., Chen, S.J., Chen, H.Y., Liao, P.C., Chen, W.J., &Wang, S.L. (2015).Prenatal Exposure to Phthalate Esters and Behavioral Syndromes in Children at 8 Years of Age: Taiwan Maternal and Infant Cohort Study. *Environ Health Perspect 123*(1), 95-100. https://doi.org/10.1289/ehp.1307154

Liu, W., Huo, X., Liu, D., Zeng, X., Zhang, Y., &Xu, X. (2014). S100β in heavy metal-related child attention-deficit hyperactivity disorder in an informal e-waste recycling area. *Neurotoxicology 45,*185-191. https://doi.org/10.1016/j.neuro.2014.10.013

Marks, A.R., Harley, K., Bradman, A., Kogut, K., Barr, D.B., Johnson, C., Calderon, N., &Eskenazi, B. (2010). Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study. *Environ Health Perspect 118*(12), 1768-1774. https://doi.org/10.1289/ehp.1002056

Mazumdar, M., Bellinger, D.C., Gregas, M., Abanilla, K., Bacic, J., &Needleman, H.L. (2011).Low-level environmental leadexposure in childhood and adult intellectual function: Afollow-up study. *Environ Health 10*(24), 1-7. https://doi.org/10.1186/1476-069X-10-24

Morabet, R.E. (2018). Effects of Outdoor Air Pollution on Human Health. Reference Module in Earth Systems and Environmental Sciences. https://doi.org/10.1016/B978-0-12-409548-9.11012-7

Nascimento, S.N., Barth, A., Göethel, G., Baierle, M., Charão, M.F., Brucker, N., Moro, A.M., Bubols, G.B.,Sobreira, J.S., Sauer, E., Rocha, R., Gioda, A., Dias, A.C., Salles, J.F., &Garcia, S.C. (2015). Cognitivedeficits andALA-D-inhibitioninchildrenexposedtomultiple metals. *Environ Res 136,*387-395. https://doi.org/10.1016/j.envres.2014.10.003

Neugebauer, J., Wittsiepe, J., Kasper-Sonnenberg, M., Schöneck, N.,Schölmerich, A., &Wilhelm, M. (2015).The influence of low level pre- and perinatal exposure to PCDD/Fs,PCBs, and lead on attention performance and attention-relatedbehavior among German school-aged children: Results from theDuisburg Birth Cohort Study. *Int J HygEnviron Health 218*(1), 153-162. https://doi.org/10.1016/j.ijheh.2014.09.005

Oulhote, Y., Steuerwald, U., Debes, F., Weihe, P., &Grandjean, P. (2016).Behavioral difficultiesin 7-year old children in relation to developmental exposure to perfluorinated alkyl substances.*Environ Int 97*,237-245. https://doi.org/10.1016/j.envint.2016.09.015

Parvez,F., Wasserman, G.A., Factor-Litvaik, P., Liu, X., Slavkovich, V., Siddique, A.B., Sultana, R.,Sultana, R., Islam, T., Levy, D., Mey, J.L., van Geen, A., Khan, K., Kline, J., Ahsan, H.,& Graziano, J.H. (2011). Arsenic exposure and motor function among children in Bangladesh. *Environ Health Perspect 119*(11), 1665-1670. https://doi.org/10.1289/ehp.1103548

Perera, F., Roen Nolte, E.L., Wang, Y., Margolis,A.E., Calafat,A.M., Wang, S., Garcia, W., Hoepner, L.A., Peterson, B.S., Rauh, V., &Herbstman, J. (2016).Bisphenol A exposure and symptoms of anxiety and depression among inner city children at 10–12 years of age. *Environ Res 151*, 195-202. https://doi.org/10.1016/j.envres.2016.07.028

Perez-Lobato, R., Mustieles, V., Calvente, I., Jimenez-Diaz, I., Ramos, R., Caballero-Casero, N., López-Jiménez, F.J., Rubio, S., Olea, N., &Fernandez, M.F. (2016). Exposure to bisphenol A and behavior in school-age children. *Neurotoxicology 53,*12-19.https://doi.org/10.1016/j.neuro.2015.12.001

Plusquellec, P., Muckle, G., Dewailly, É., Ayotte, P., Bégin, G., Desrosiers, C., Després C., Saint-Amour, D.,&Poitras, K. (2010).The relation of environmental contaminants exposure to behavioral indicators in Inuit preschoolers in Arctic Quebec. *Neurotoxicology31*(1), 17–25. https://doi.org/10.1016/j.neuro.2009.10.008

Pujol, J., Martínez-Vilavella, G., Macià, D.,Fenoll, R., Alvarez-Pedrerol, M., Rivas, I.,Forns, J., Blanco-Hinojo,L., Capellades, J., Querol, X., Deus, J.,&Sunyer, J. (2016).Traffic pollution exposure is associated with altered brain connectivity in school children. *Neuroimage 129*,175-184. https://doi.org/10.1016/j.neuroimage.2016.01.036

Rauh, V.A., Garcia, W.E., Whyatt, R.M., Horton, M.K., Barr, D.B., &Louis, E.D.(2015).Prenatal exposure to the organophosphate pesticide chlorpyrifos and childhood tremor. *Neurotoxicology 51,*80-86. https://doi.org/10.1016/j.neuro.2015.09.004

Rauh, V.A., &Margolis, A.E. (2016).Research Review: Environmental exposures, neurodevelopment, and child mental health-new paradigms for the study of brain and behavioral effects. *J Child PsycholPsychiatry 57*(7), 775-793. https://doi.org/10.1111/jcpp.12537

Rivas, I., Querol, X., Wright, J., &Sunyer, J. (2018).How to protect school children from the neurodevelopmental harms of air pollution by interventions in the school environment in the urban context. *Environ Int 121*,199-206. https://doi.org/10.1016/j.envint.2018.08.063

Rodríguez-Barranco, M., Lacasaña, M., Gil, F., Lorca,A., Alguacil,J., Rohlman, D.S.,González-Alzaga, B., Molina-Villalba, I., Mendoza, R., &Aguilar-Garduño, C. (2014).Cadmium exposure and neuropsychological development in school children in southwestern Spain.*Environ Res134,*66-73. https://doi.org/10.1016/j.envres.2014.06.026

Roen, E.L., Wang, Y., Calafat, A.M., Wang, S., Margolis, A., Herbstman, J.,Hoepner, L.A., Rauh, V., &Perera, F.P. (2015).Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age. *Environ Res 142,*739-745. https://doi.org/10.1016/j.envres.2015.01.014

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., &Korrick, S.A. (2010).Prenatal Organochlorine Exposure and Behaviors Associated with Attention Deficit Hyperactivity Disorder in School-Aged children. *Am J Epidemiol 171*(5), 593-601. https://doi.org/10.1093/aje/kwp427

Shelton, J.F., Geraghty, E.M., Tancredi, D.J., Delwiche, L.D., Schmidt, R.J., Ritz, B.,Hansen, R.L., &Hertz-Picciotto, I.(2014).Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. *Environ Health Perspect122*(10), 1103–1109. https://doi.org/10.1289/ehp.1307044

Šovčíková,E., Wimmerová,S., Strémy, M., Kotianová, J., Loffredo, C.A., Murínová,L.P., Chovancová, J., Čonka, K., Lancz, K.,&Trnovec, T. (2015). Simple reaction time in 8-9-year old children environmentally exposed to PCBs. *Neurotoxicology 51,*138-144. https://doi.org/10.1016/j.neuro.2015.10.005

Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., López-Vicente, M.**,**Suades-González. E., Foraster. M., Garcia-Esteban, R., Basagaña, X., Viana, M., Cirach, M., Moreno, T., Alastuey, A., Sebastian-Galles, N., Nieuwenhuijsen, M.,&Querol, X. (2015).Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study. *PloS Med 12*(3), 1-24. https://doi.org/10.1371/journal.pmed.1001792

Sunyer, J., Suades-González, E., Garcia-Esteban, R., Rivas, I., Pujol, J., Alvarez-Pedrerol, M., Forns, J., Querol, X.,&Basagaña, X. (2017).Traffic-related Air Pollution and Attention in Primary School Children: Short-term Association. *Epidemiology 28*(2), 181-189. https://doi.org/10.1097/EDE.0000000000000603

Tewar, S., Auinger, P., Braun, J.M., Lanphear, B., Yolton, K., Epstein, J.N., Ehrlich, S., &Froehlich, T.E. (2016).Association of Bisphenol A exposure and Attention-Deficit/ Hyperactivity Disorder in a national sample of U.S. children. *Environ Res 150,*112-118. https://doi.org/10.1016/j.envres.2016.05.040

Tran, N.N., Pham, T.T., Ozawa, K., Nishijo, M., Nguyen, A.T.N., Tran, T.Q.,Hoang, L.V., Tran, A.H., Phan, V.H.A., Nakai, A., Nishino, Y.,&Nishijo, H. (2016). Impacts of Perinatal Dioxin Exposure on Motor Coordination and Higher Cognitive Development in Vietnamese Preschool Children: A Five-Year Follow-Up. *PLoS One11*(1), 1-15. https://doi.org/10.1371/journal.pone.0147655

Vuong, A.M., Yolton, K., Webster, G.M., Sjödin, A., Calafat, A.M., Braun, J.M.,Dietrich, K.N.,Lanphear, B.P., &Chen, A. (2016).Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children. *Environ Res 147,*556-564. https://doi.org/10.1016/j.envres.2016.01.008

Vuong, A.M., Yolton, K., Xie, C., Webster, G.M.,Sjödin, A., Braun, J.M., Dietrich, K.N.,Lanphear, B.P.&Chen, A.(2017). Childhood polybrominated diphenyl ether

(PBDE) exposure and neurobehavior in children at 8 years. *Environ Res 158*, 677-684. https://doi.org/10.1016/j.envres.2017.07.028

Wasserman, G.A., Liu, X., Parvez, F., Factor-Litvaik, P., Ahsan, H., Levy, D., Kline, J., van Geen, A., Mey, J., Slavkovich, V., Siddique, A.B., Islam, T.,&Graziano, J.H. (2011). Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology 32*(4), 450-457.https://doi.org/10.1016/j.neuro.2011.03.009

Wasserman, G.A., Liu, X., Parvez, F., Factor-Litvaik, P., Kline, J., Siddique, A.B., Shahriar, H., Uddin, M.N., van Geen, A, Mey, J.L., Balac, O.,&Graziano, J.H. (2016). Child Intelligence and Reductions in Water Arsenic and Manganese: A Two-Year Follow-up Study in Bangladesh. *Environ Health Perspect 124*(7), 1114-1120. https://doi.org/10.1289/ehp.1509974

Zhang, H., Yolton, K., Webster, C.M., Sjödin, A., Calafat, A.M., Dietrich, K.M.,Xu, Y., Xie, C.,Braun, J.M., Lanphear, B.P.,&Chen, A. (2017).Prenatal PBDE and PCB Exposures and Reading, Cognition, and Externalizing Behavior in Children. *EnvironHealthPerspect*, *125*(4), 747-752. https://doi.org/10.1289/EHP478