# ENDOCRINE DISRUPTING CHEMICALS AND FETAL NEURODEVELOPMENTAL DISORDERS

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# Equal contribution

## Abstract

*Endocrine Disrupting Chemicals (EDC) is a heterogeneous group of substances that act on steroid receptors, inducing genetic, epigenetic and cellular changes. Their action is validated in all organs with steroid receptors, the effects of which vary depending on the time of exposure.*

*Neurodevelopmental disorders have experienced a significant increase in recent decades, most carefully studied problems being Autistic disorders and Attention Deficit Hyperactivity Disorder. Although these disorders are multifactorial, it appears that in utero exposure to EDC influences neurogenesis and nerulation processes, creating the premise of neurobehavioral disorders.*

*The purpose of this papaer is to review the effects of the main classes of endocrine substances on the fetal nervous system that may lead to neurodevelopment disorders.*

## Rezumat: Disruptorii endocrini şi tulburările de neurodezvoltare

*Endocrine Disprupting Chemicals (EDC) constituie un grup heterogen de substanţe care acţionează pe receptorii steroizi, inducând modificări la nivel genetic, epigenetic şi celular. Acţiunea acestora se validează la nivelul tuturor organelor care prezintă receptori steroizi, efectele acestora fiind variate în funcţie şi de momentul expunerii.*

*Tulburările de neurodezvoltare au cunoscut o creştere importantă în ultimele decenii, cele mai atent studiate afecţiuni fiind cele autistice şi Tulburările de hiperactivitate cu deficit de atenţie. Deşi aceste afecţiuni sunt multifactoriale, se pare că expunerea in utero la EDC influenţează procesele de neurogeneză şi nerulaţie intrauterine, creând premisele unor afecţiuni neurocomportamentale.*

*Scopul acestei lucrări este de a trece în revistă efectele principalelor clase de substanţe endocrine asupra sistemului nervos fetal care pot conduce la tulburări de neurodezvoltare.*

**Cuvinte cheie:** Disruptori endocrini, Neurodezvoltare, Autism, ADHD

## Introduction

The increase in the prevalence of neurodevelopment disorders in recent decades, particularly autism spectrum disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD), has led to a more careful research into the etiology and risk factors involved in these pathologies.

Neurodevelopment disorders are a group of disorders characterized by impairment of social

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aptitudes or intelligence during early childhood and are subclassified into intellectual disability (intellectual development disorder), communication disorders, ASD, ADHD, specific learning disabilities and motor disorders[1].

Fetal central nervous system (CNS) development is a complex process starting approximately from the 18th day of intrauterine life and it is based on a series of biological processes including proliferation, migration, neuronal differentiation and synaptogenesis occurring in a well-established sequence[2].

Researchers' attention was drawn to neurodevelopmental pathologies, especially ADHD and ASD, mainly due to the fact that they have childhood onset, pointing towards a possible intrauterine neurological trigger. Some of these disorders have an unequal gender distribution, for example, conditions such as ADHD and autistic-like behaviors are more common in boys, whereas girls are more likely to have anxiety and depression disorders, indicating a possible involvement of sex hormones in these pathologies[5]. Interactions between genetic, environmental and social factors are an important determinant of brain development and cognitive behavior[5].

Numerous articles highlight the impact of environmental risk factors in pregnancy or infancy, which can influence future childhood and adulthood health status[3]. Studies regarding the harmful effects of environmental pollutants on fetal neurodevelopment began with the description of nicotine- and cigarette-induced changes on the fetal wellbeing, with recent evidence of a possible association between these substances and the development of emotional disturbances or attention deficit[4].

EDCs are a group of endogenous substances defined as "exogenous agents that interfere with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body, hormones responsible for maintaining homeostasis and regulating physiological processes[6].

EDCs are a complex class, which includes many substances harmful to the human body, such as Bisphenol A (BPA), phthalates, pesticides, polychlorinated biphenyls (PCBs) and heavy metals. These agents are commonly found in cosmetics, pharmaceutic products and even in food[7] and can easily enter the human body by ingestion, inhalation and even transdermally. They are then deposited in certain tissues and their harmful effects can be validated in the current or even future generations[7].

EDCs have complex mechanisms of action which can influence the affinity of hormone receptors in all tissues in the body and these effects seem to take place already during intrauterine life. The transplacental passage of these substances has been demonstrated by several studies which highlighted the presence of EDCs in the fetal central nervous tissue[8]. Fetuses are more affected than adults by exposure to EDCs given their decreased hepatic metabolization of these compounds by an yet immature enzymatic system[9]. At the same time, the harmful effects of EDC are validated according to the organogenetic period in which they take action. Substance consumption resulting in neurogenesis imparement has been constantly linked to the neuro-behavioral disorders[10].

The most studied neurodegenerative diseases caused by EDC are ASD and ADHD, with a large body of evidence favouring the association between these pathologies and certain classes of EDCs.

Autistic disorders have a polygenic and multifactorial etiology and typically arise from the complex interactions between certain genetic defects and intrauterine exposure to environmental factors causing a disruption of neurodevelopment and cortical processes[11,12].

Attention Deficit Hyperactivity Disorder is a mental disorder resulting from a neurodevelopmental trigger and it's characterized by attention problems, excessive activity or behavioral control difficulties that are not appropriate to the age of a person[13].

## How EDCs affect the CNS development

Brain development extends from the beginning of embryonic life to adolescence, and any disruption of this complex process can have serious and long-lasting consequences on the brain structure

and function resulting in a variety of neurodevelopmental disorders. The fetal brain is subject to continuous intrauterine changes and it is common knowledge that steroid receptors play an important role in the migration process of neurons, neuronal differentiation and formation of new synapses[14]. Imparement of the neurulation, neuronal proliferation, differention and migration processes, or changes in the synaptogenetic[15] and neurotransmitter systems can lead to behavioral or cognitive deficits[16].

Synaptogenesis appears to be a particularly sensitive period in the neurodevelopment process, given its molecular complexity and long duration - it spans from early gestation to adulthood[10].

EDCs can stimulate the migration and acceleration of the differentiation of glutamatergic (excitatory) and gabbergic neurons (inhibitors) by means of an estrogen-like effect [17].

One of the best-understood and extremely well organized synapses is the excitatory or glutamatergic synapse[17]. This also serves to support and mediate a series of critical neuronal processes for synaptic transmission and neuronal plasticity, and its impairment can lead to conditions such as mental retardation or neurobehavioral disorders such as autism[18] and ADHD[19].

Neuronal migration and neurogenesis may be influenced by EDCs through a nicotine-like mechanism, which can induce a reduction in the number of glutamatergic neurons in the medial prefrontal cortex and disruption of neuronal progenitor cell cycles in ventricular and subventricular areas[20], changes susceptible to behavioral disorders.

Stimulation of glutamatergic neurons in certain brain areas such as the hypothalamus and the hippocampus may lead to alterated eating behaviours[21], the association between neurobehavioral disorders and obesity being well known.

The hypothalamus is the center that coordinates homeostatic functions such as stress, emotion, reproduction, feeding habits and regulates the production and circulation of sex hormones in the body[22]. In rodents, sexual dysmorphisms in the hypothalamic regions appear during the perinatal period being caused by an interruption of estrogen signaling at this level. This is presumed to be one of the main mechanisms underlying neuroendocrine changes triggered by EDCs [23].

At the same time, the hippocampus is susceptible to the action of EDCs, mainly amprenting cognitive functions and IQ, due to the importance of this region of the brain in processes such as memory and learning[24].

EDCs can also interfere with the synthesis, transport and release of neurotransmitters that can alter complex neurodegenerative and cognitive processes such as memory, learning and attention, thus leading to the onset of certain conditions such as ADHD or ASD[21]. Among these neurotransmitters are dopamine, serotonin, norepinephrine and glutamate, which play an important role in behavioral, cognitive, learning and memory processes[25].

The prototype of this class are pesticides, especially organophosphorus pesticides, whose mechanism of action consists in altering the synthesis and release of neurotransmitters, and ultimately in neurotoxicity[26]. Several studies have highlighted a link between agricultural areas and a reduction in IQ, attention deficit or human interrelation behavioral disorders in the early years of life[26–28].

A central role in neuro-behavioral EDC changes seems to be caused by an alteration in thyroid hormone metabolism and their mode of action[29]. It is well-known the effect of thyroid hormones on neuronal migration and myelinization, which is validated both in the intrauterine life and in childhood[29].

Also another important link by which EDCs act on the nervous system is the alteration of local oxidative stress[30]. Oxidative stress is defined as a change in the balance between pro-oxidant molecules and antioxidants that results in long-term lesions, a mechanism by which environmental factors influence the genetic susceptibility[30].

Along with oxidative stress, epigenetic mechanisms such as DNA methylation, histone changes and microRNA alterations can induce changes in fetal neurogenesis by modifying genetic expression[31]. Epigenetic mechanisms play an important role in brain development. In particular, DNA methylation, disorders in the establishment,

maintenance or reading of methylated DNA may be associated with neurodevelopmental disorders[32].

Furthermore, in a study from 2016, LaRocca et al. described the cytotoxic effects of EDCs through the changes in the placental microRNA[33], effects which can be different according to the fetal gender. These effects of EDCs differ according to fetal sex because the placenta expresses different isoforms of certain receptors according to fetal gender, and autophagia processes also differ between male and female fetuses[34].

**Bisphenol A (BPA)**

Bisphenol A is considered the prototype of non-steroidal estrogens, which interferes with the estrogen receptors at nuclear level. However, its binding affinity to the estrogen receptor was found to be lower than that of 17b-estradiol[35] and the harmful effects of BPA are manifested through its metabolites such as 4-methyl-2,4-bis (4-hydroxyphenyl) pent-1-ene (MBP)[36].

It is used in the production of a variety of chemical products such as polycarbonate plastic and epoxy resin[7], and as such the most important route of entering the body is oral. Respiratory or transdermal routes are also possible[37].

BPA can induce changes in the endocrine system by interacting with estrogen, androgen, or thyroid receptors[38]. Antenatal exposure of mice to BPA reduces synaptogenesis and synaptic proteins, causes changes in synapse structure, thus affecting behavior and memory, these effects being especially demonstrated in male rodents[15]. Furthermore, exposure to BPA may cause neural changes and changes in the glial tissue which also affect predominantly male subjects[39].

BPA may cross the placenta and it seems that its presence in maternal urine is associated with hyperreactivity and aggressiveness in children[40]. In a study published in 2009 by Braun et al. they demonstrated that children aggressiveness and hyperreactivity are directly proportional to gestational concentrations of BPA[40].

In a another study using the same cohort of patients, the authors have shown that attention disturbances and hyperreactivity affect girls rather than boys, suggesting the possibility of a different behavior in adulthood[41]. However, the results of this study are disapproved by a more recent publication from 2015 by Casas et al., who reported that prenatal BPA concentrations were associated with an increased risk of ADHD-like behaviors especially in boys[42].

There are researchers who report aggressive behaviors, but also learning difficulties and anxious and depressive disorders in children exposed to Bisphenol A in utero [43,44].

Several studies reported a correlation between mean urinary BPA concentration and ASD cases compared to control groups, some of them after removal of confounding factors such as age, body mass index (BMI), sex, and renal function of patients[45–47].

**Phthalates**

Phthalates are diesters of 1,2-benzenedicarboxylic acid (phthalic acid), a group of chemicals used as plasticizers for vinyl polychlorinated plastic materials[7]. Phthalates reach the human body by ingestion, inhalation or cutaneous absorption[48] and have the ability to cross the placental barrier, especially those with low molecular weight, their presence being demonstrated in newborn meconium and urine[49]. In addition to placental passage, there are studies that support the transfer of phthalates into breast milk thus validating their harmful effects in the neonatal period[50].

Phthalates act as EDCs, having both estrogenic and anti-androgenic activity[51]. They have a reduced effect in vitro on androgen receptors (AR), suggesting that phthalates are not direct antagonists of these receptors[52]. It is known that phthalates have a short half-life and their harmful effects occur through chronic and long-term exposure.

In rodent experimental models maternal exposure to DEHP (di (2-etilhexil) ftalat) decreases the concentration of free cholesterol and sphingomyelin, substances that play an important role in neurodevelopment[53]. They may cause disruption at the neuro-endocrine level (impairment of estrogen,

androgen and thyroid hormones), may induce changes in dopaminergic neurons in the midbrain and thus affect the differentiation of neurons that lead to ADHD[54] or may cause placental micro-RNA damage and epigenetic expression alteration[33,55].

This mechanism was also described in a study from 2010 by Adibi et al., who analyzed phthalate induced placental transcriptional changes using placentas harvested from 54 vaginal deliveries and proved a direct relationship between these changes and urinary concentrations of phthalates[56].

Exposure to phthalates leads to neurodegenerative disorders such as ADHD[57], autistic-like disorders[58,59], cognitive problems with lower IQ and sometimes psycho-affective disorders [60,61].

Phthalates may lead to neurological and neurobehavioral disorders through an indirect mechanism also, namely the increased risk of premature birth in patients exposed to these substances[62]. There is a positive correlation between urinary concentrations of phthalate metabolites and preterm delivery before 37 weeks, both through the risk of premature labor and the risk of premature rupture of the membranes[63]. A possible explanation for these induced changes is given by the pro-inflammatory effect of phthalates in the body which has been demonstrated both in vivo and in vitro[64].

At the same time, phthalates may induce oxidative stress changes, especially at the beginning of organogenesis when embryos are particularly sensitive to toxic injuries due to the transition from anaerobic to aerobic metabolism, which coincides with maturation of mitochondrial structure and function[65]. This could reflect older observations that antioxidant enzyme activity is connected with the onset of organogenesis and at the beginning of this process the embryo cannot adequately protect itself from oxidative imbalances[65,66].

## Pesticides

Pesticides are a class of harmful substances designed to destroy pests and improve agriculture, but the side effects of this class were not delayed, Rachel Carson being the first person to highlight their harmful effect on the enviroment[67].

The adverse outcome of their use is validated during gametogenesis and early fetal development[68], because the highest rate of transfer of these chemicals to the fetus is due to the mobilization of the maternal fat reserve during pregnancy[69] and breastfeeding[70]. Pesticides can cross the placenta based on their liposolubility, and because of the immaturity of the hematoencephalic barrier during intrauterine life they can validate their harmful effects very early in life[71]. The lipophilic properties of many pesticides make it possible to concentrate them in organs with high fat content, such as the brain[71].

Newborn and children are extremely vulnerable to pesticides, which can cause a wide range of side effects on intellectual function[72] and central nervous system development[73]. Several epidemiological studies have described an association between pesticides exposure and neurological and psychiatric disorders in children and adults. Pesticides exposure may be associated with an increased risk of ASD-like[28,74], ADHD[30,79], memory / learning and motor disorders[26,76].

## Organochlorine pesticides

Exposure to organochlorinated pesticides (OC) has been associated with neurological adverse effects for over 40 years, the class exponent being DTT (Dichlorodiphenyltrichloroethane). OCs are liposoluble compounds that can penetrate the neuronal membrane, alter depolarization and increase neuronal excitability[2,76]. The pre and postsynaptic changes created by OCs and the alterations in the GABAergic, glutamatergic and dopaminergic responses in areas such as the prefrontal cortex and in the brain substantia nigra can induce behavioral changes and damage to cognitive and motor areas[2,76].

Also, these substances have a neurodegenerative effect. By affecting cerebral and cerebellar regions they can induce tremors and convulsions with the occurrence of Parkinson's disease[77].

Numerous studies associate OC pesticides exposure with reduced cognitive function and impaired memory[72,78], an impairment in reflexes and motor

function especially of fine movements[79], attention disorders[27,75] and ASD[74].

### Organophosphorus pesticides

Organophosphorus pesticides (OP) have as central mechanism of action the inactivation of acetylcholinesterase and enzyme phosphorylation[2]. Acetylcholinesterase is an enzyme that carries out hydrolysis of acetylcholine - a neurotransmitter found in cholinergic synapses in the central and peripheral nervous systems - thus preventing over-stimulation of muscarinic and nicotinic receptors[2]. OPs therefore act as inhibitors of acetylcholinesterase, increasing both the concentration and the time of action of acetylcholine in the body and causing cholinergic hyperactivity and spasms in the smooth and striated muscles[2].

During fetal development, the neurological effects of OP exposure, even at low doses, may affect neurotransmitters, including acetylcholine, which play essential roles in cellular and architectural development of the brain[80].

In addition to their anticholinergic effect, OPs can also act by interrupting or interfering with different cellular processes: DNA replication, axonal and dendritic growth, and oxidative stress impairment in the developing brain[81]. For example, infants exposed prenatally to a commonly used OP pesticide (chlorpyrifos) showed abnormal changes in brain areas related to attention and receptive language, social knowledge, reward, emotion, and inhibitory control[82].

The effects of OP pesticides on IQ[82,83], cognitive deficits[82], reflexes[84,85] and attention disturbances[86,87] or ASD[88] appear as early as childhood and aggravate with aging. The first changes that can be highlighted are reflexes and attention deficits[85].

### Polychloro-biphenyls (PCBs)

Polychlorinated biphenyls were once widely used in cooling fluids, electrical equipment and in the manufacture of electrical insulators[89]. These are chlorinated organic compounds that have been banned since the 80s due to their pollutant effect and long life span in nature[89]. PCBs are lipophilic substances and therefore can cross the placental barrier and be excreted in breast milk[90,91]. Their effects as EDCs are mainly manifested by neurotoxicity[92] and thyroid hormone alteration both directly and through their metabolites, hydroxylated PCBs (OH-PCBs), because their chemical structure is similar to that of thyroid hormones[93].

It has been proven in rodent models that PCB metabolites can induce changes in hyperreactivity and motor abnormalities[94,95], due to inhibition in the development of dendrites in cerebellar Purkinje cells[96]. Also, in a more recent study using rodent models exposed to Aroclor 1254 authors demonstrated that this substance disrupts the maturation development of synaptic excitatory neurons in newborns, especially those from the hippocampus region, which are involved in learning and memory, thus explaining later behavioral changes[97].

In humans, intrauterine exposure to PCB may be associated with learning disorders, low IQ[98], ADHD[99] and autism[100]. The prevalence of these pathologies has been on the rise in the past decades.

### Heavy metals

Mercury and lead are two heavy metals that have been extensively studied, being considered to act as endocrine disruptors and to have negative effects on neurodevelopment. The most common exposure to these two metals occurs through the use of cosmetics and the consumption of fish during pregnancy, these metals being able to cross the placenta[101,102]. Exposure to heavy metals, in particular lead and mercury, causes neuronal changes by methylation of DNA and can thus induce neurobehavioral and neurodegenerative changes[103,104].

#### *Lead*

Lead is the most abundant heavy metal on earth, the main sources of lead exposure are paints, dust, soil, kitchen utensils and gasoline. Exposure to lead even at low doses has been associated with a

number of adverse health effects, cognitive and behavioral disorders[105]. Lead exposure may lead to learning and memory disorders in mice through several pathways: synapse changes, synaptic gene regulation, insulin degradation enzyme (IDE), insulin 2-like growth factor (IGF2) amyloid 40 (Ap 40) and tumor necrosis factor (TNF-α)[106]. Similar to studies in mice, a study on human neurons has shown that lead exposure may increase the expression of serine / threonine protein phosphatases, changes are associated with impairment of learning and memory[107]. Intrauterine exposure to lead is associated with cognitive impairment[108], decreased IQ[109], ADHD[110]. Folowing transplacental passage, lead gradually accumulates in fetal tissues, preferentially in the brain[111].

### *Mercury (Hg)*

Depending on its chemical form, mercury (Hg) can be very toxic. Occupational exposure leads to neurodegenerative disorders, behavioral changes and even death[102]. The most common way of contamination is through fish and seafood widely consumed by pregnant women given their abundance in polyunsaturated fatty acids[102].

Rodent exposure to mercury is associated with changes in the dopaminergic system and ADHD type disorders[102,112], but also with learning disabilities[113].

In humans, in utero exposure to mercury leads to ADHD and ASD, but this association is often contradictory, because of the beneficial effect of omega 3 fatty acids on fetal neurodevelopment[114]. The harmful effect of Hg on neurodevelopment and the association with pathologies such as ADHD is possible, this correlation being stronger in studies that have controlled error factors such as the concentration of omega 3 and omega 6 fatty acids in the blood[115]. These studies also demonstrated that a high consumption of meat fish overrides the harmful effects of mercury[102,115].

## Conclusions

The harmful effects of EDCs on fetal neurodevelopment are highly dependent on the time of exposure, some periods of fetal development being more susceptible than others. The link between exposure to EDCs and neuro-behavioral pathologies is clear for most toxic categories, but their mechanisms of action are not yet fully elucidated, and the mode of action on animal models may be different in humans. Also, neither the effects nor the mode of action of simultaneous exposure to several classes of EDCs are known because they can act through different mechanisms or enhance their mutual effects.

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