

# Environmental pollution and the fetus

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## Abstract

A child is a growing and developing human being early from conception throughout the end of adolescent period. Children at any stages of growth and development need to be protected from environmental health hazards. They need safe and health promoting environment to reach their optimum growth and development that they are capable genetically. However physical, chemical, biological and social environments have changed throughout decades and children of today are living in a very different environment than from their grandparents and parents. Today they are at most risk of being exposed to new chemicals that are mostly not tested for fetus and children. Since World War II, approximately 80,000 new synthetic chemicals have been manufactured and released into the environment in large amounts, with 10 new chemicals being introduced every day. The vast majority of these chemicals have not been studied adequately for their impacts on human health or their particular impacts on fetus. Many of these synthetic chemicals are persistent and bio-accumulative, remaining in the human body long after the exposure. Parental exposures occurred before the conception threatens the fetus both because the maternal or paternal reproductive organs are affected and because chemicals that can be accumulated in the mother's body before pregnancy may be mobilized and cross over placental barrier during pregnancy. Many synthetic chemicals are already present in cord blood and we do not know how these multi-chemical exposures affect programmed development of fetus and studies are limited on long term effects of single chemical exposure. Some examples of health effects resulting from developmental exposures include those observed prenatally and at birth such as miscarriage, stillbirth, low birth weight, birth defects. Establishing a causal links between specific environmental exposures and complex multifactorial health outcomes is difficult and challenging.

## Keywords

Fetus, development, environmental pollution.

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## Introduction

In a 2004 study led by the Environmental Working Group (EWG) in the US, the presence of 413 different environmental toxins were examined in the cord blood from a total of 10 randomly selected newborns from different hospitals, and overall 287 of these toxins tested positive with an average of approximately 200 toxic chemicals detected in each cord blood sample [1]. Among these are several substances defined as “carcinogens” by the Environment Protection Agency (EPA) such as eight different type of perfluorinated chemicals used in fast food industry (due to their water and grease resistance) and textile/fabric industry (including teflon chemicals); dozens of brominated chemicals used for flame retardation and their by-products; and pesticides. One-hundred eighty of these 287 chemicals have previously been reported to cause cancer in human and animals, 217 have been associated with birth anomalies, and 217 are neurotoxic [2]. This piece of information directly calls into the question the effects of this mixture of toxic substances on the developing fetus, with possibly dreadful answers due to the fact that prenatal exposure might be associated with more serious, permanent, and/or irreversible damage as compared to exposure in later stages of life. This complex mixture incorporating hundreds of different carcinogenic, neurotoxic, and developmental toxic chemicals in the cord blood has not been very well studied in terms of its impact on the programmed fetal growth and on the later stages of development.

On a daily basis, the background exposure to environmental pollutants is mostly due to phthalates, plastic products such as bisphenol A, polychlorinated biphenyls (PCBs), lead, mercury, cadmium, asbestos, dioxins, polyhalogenated aromatic hydrocarbons (PHAHs), solvents, pesticides, inhaled toxins (tobacco smoke, ozone, particulate matter), and chlorinated disinfection byproducts (DBPs). Most of these chemicals are “endocrine disruptors”; in other words, they are chemical substances that disrupt the production, release, transport, binding, and/or breakdown of natural hormones that are essential for the growth and development at the time of conception and thereafter. Chronic low dose exposure to certain endocrine disruptors may lead to developmental functional disorders that are not observed with high dose exposure [3]. The multifactorial nature of the emergent health effects is a major obstacle to establish a cause and effect relationship for an individual environmental toxin. Also the term “environmental” is usually regarded

as a vague, arbitrary, and subjective attribute when it comes to define a pathological condition.

Information on the impact of these environmental toxins on human health – or in other words for establishing a relationship between possible health effects and environmental factors – comes from studies examining the long term effects of chemical exposures due to accidents or natural disasters; occupational; animal and epidemiologic studies.

## Preconception exposure

Studies have shown that toxic chemical substances may influence human development even before conception. Toxic effects on the fetus occur via parental and/or maternal exposure before conception or maternal exposure during pregnancy. Environmental chemical pollution passes to the next generation through placenta or during lactation. Fat soluble toxic chemical pollutants may accumulate in maternal fat tissue long before conception and across placenta, eventually affecting embryo and fetus. Dioxin, lead and organochlorine pesticides may show similar pre-conceptional maternal accumulation. Therefore even in the absence of maternal toxic exposure during pregnancy, fetal development may be affected by previous accumulation and eventual release of toxic substances during pregnancy. Epidemiological studies suggest an increased incidence of spontaneous abortion, congenital abnormalities, and childhood neoplasias in the case of paternal occupational exposure to heavy metals, combustion products, solvents, and pesticides (e.g. in case of fireman, automobile mechanics, welding, and dying) [4, 5]. However establishing a cause and effect relationship presents significant challenges not only due to conflicting data but also due to the fact that such effects might result from a very wide variety of causes.

Preconception paternal exposure to heavy metals such as lead and mercury increases the risk of spontaneous abortions [6], and occupational paternal exposure to lead has been associated with infertility, stillbirth, and spontaneous abortion [7]. Similarly, preconception occupational exposure to metal dust and smoke during welding has been associated with preterm births [8]. In two other studies, despite the absence of a significantly increased risk of spontaneous abortions, paternal solvent exposure caused an increased incidence of congenital anomalies [9, 10]. Also, the risk of congenital anomalies increased in babies whose fathers worked in a laboratory environment [11]. Limited data also suggest an association between paternal 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure

and neural tube defects [12]. Paternal onset of smoking at an early age associated with increased body mass index in the son, and alcoholism was found to decrease birth weight [13, 14].

Again, preconception paternal exposure to pesticides has been reported to cause an increased risk of acute lymphoblastic leukemia [15, 37]. Although some studies suggest an increase in the risk of leukemia or lymphoma with preconception paternal exposure to solvents, other findings do not suggest a significant association [16-19]. The effect of paternal chemical exposure on the fetus occurs via several routes including mutagenic and epigenetic mechanisms within the sperm, and transfer of chemicals within the sperm to the mother [20].

### Placental transfer

The amount of placental transfer of toxic chemicals into fetus depends on the distinctive characteristics of the chemical substance and placenta. Placental permeability to toxic substances is determined by several factors including placental blood flow and metabolism, thickness, surface area, lipid/protein content of the membrane and transport systems, all of which are in a continuous state of changes during pregnancy. Importantly, placental permeability to toxic substances also differs between species, unfortunately jeopardizing the reliability and value of animal studies in reaching conclusions regarding human safety [21]. Non-ionized fat soluble chemicals with low molecular weight (< 1,000 Daltons) exhibit a very rapid placental transfer, largely regulated by placental blood flow [22]. Another possible means of repeated fetal exposure is through the amniotic fluid. For instance several plastic and pesticide chemicals may accumulate in the amniotic fluid following urinary excretion. After the fifth month of the pregnancy, fetus has regular swallowing and breathing movements, leading to the flow of amniotic fluid into the lungs and gastrointestinal system that result in a vicious cycle of repeated exposure to chemicals [22].

Chemical substances are transferred to fetal circulation if they are not metabolized by maternal and/or placental metabolism. Although some placental metabolism occurs via Phase I oxidative (CYP cytochrome P450) and Phase II conjugation enzymes (some of which are inactive), this is less efficient as compared to the hepatic metabolism. Organochloride pesticides, cigarette smoke, and certain medications have been shown to induce placental CYP1A1. Placental Phase II enzymes also include glutathione transferase, epoxide hydrolase, N-acetyltransferase,

sulfotransferase, and UDP-glucuronyl transferase. Generally, there is an increase in the activity of these enzymes with the progression of pregnancy. However, placental metabolism may even be harmful to the fetus as it may be associated with the production of some carcinogenic metabolites. For example, placental enzymes are known to produce certain reactive metabolites that may react with DNA and result in developmental disorders or diseases [23].

Toxic and/or foreign substances may disturb placental function through their effect on a multitude of processes including implantation, cellular growth and maturation, signal pathways, release and production of hormones and enzymes, transport of nutrients and waste products, and finally functions during birth. A potential threat on placental function may translate into adverse consequences such as preterm births, congenital abnormalities, and stillbirths [23]. Placenta plays a major endocrine role during pregnancy, increasing its vulnerability to endocrine disrupting chemicals. Organochlorine pesticides, most of which have endocrine disrupting effects, are frequently detected in placental tissues, allowing them to be utilized as a general marker for the level of placental exposure to environmental toxins [21, 24].

### Fetal effects

Following the transfer of chemical substances from placenta to fetal circulation, a fetal attempt to metabolize these chemicals occurs through isoenzyme groups, some similar and some dissimilar to adults. Progress of pregnancy is associated with increased enzyme activity in the fetus. Although fetal liver is responsible for most of the fetal metabolism, other organs such as adrenal glands, kidneys, lungs, and brain may also contribute [25]. However, enzyme activity responsible for the catalysis of Phase I and II reactions is much weaker compared to adults that may lead to excessively higher fetal blood levels as compared to those in the maternal circulation due to significantly lower capacity of the fetus for detoxification and excretion. Unfortunately fetal blood-brain barrier is also immature, leading to increased vulnerability of the fetal brain to effects of toxic chemicals.

Fetal exposure to toxic chemicals can be assessed using meconium and cord blood samples. Also presence of toxic chemicals in breast milk is used as an indicator for fetal exposure [26].

Intrauterine exposure to a single chemical pollutant at a “no observed adverse effect level” (NOAEL) may result in no adverse consequences. Traditional toxicity tests unfortunately only examine the effect of a single

chemical pollutant. On the other hand, intrauterine fetal exposure involves many chemicals which may lead to fetal abnormalities through synergistic or incremental effects despite exposure at NOAEL for individual toxins.

When pregnant mice were administered a mixture containing DEHP (a phthalate), pesticides (vinclozolin, prochlorax) and finasteride (a medication), each at NOAEL, an endocrine disrupting effect (interfering with the production, release, transportation, binding and breakdown of natural hormones in the body) was observed with an accompanying reduction in the anogenital distance, a significant marker of male feminization [26, 27].

Timing of exposure to toxic chemicals is also important. Due to variable susceptibility of fetal tissues and organs at different stages of fetal development, the same toxic substance may result in different effects depending on the time of exposure. For example since cellular growth occurs at a faster rate during embryologic development, exposure at this stage is more likely to cause mutations or congenital anomalies. While thalidomide exposure at day 26 after conception at a dose of 50 mg results in congenital anomaly (phocomelia), exposure at week 10 with the same dose is not associated with anomalies [28].

Exposure to organic solvents has been associated with spontaneous abortion, however a meta-analysis did not confirm this conclusion [29]. A ubiquitous chemical with estrogenic effects, 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin, was found to increase the risk of fetal death and low birth weight in animal studies [30, 52]. An increased serum DDT/DDE level was also associated with increased risk of abortion [31]. A concentration of arsenic above 100 µg/l in water resulted in early or late fetal deaths [32]. Similarly, maternal lead exposure was associated with early fetal deaths and preterm births [33, 34]. Another study found a dose-response relationship between maternal blood lead levels in the first trimester and early fetal deaths, even with maternal lead concentrations as low as 5-9 µg /dl [35]. Again, some studies found increased risk of preterm births despite relatively lower maternal blood lead levels [36, 37]. Maternal smoking during pregnancy is associated with increased incidence of abortus and still births [38] as well as a two-fold increase in the risk of low birth weight and intrauterine growth retardation [39, 40]. Prenatal organochlorine exposure was also found to be associated with low birth weight [41], and similarly prenatal exposure to bisphenol A associated with low birth weight and intrauterine growth retardation in addition to disruption in adipokine activity in the newborn [42].

Epidemiologic studies showed a relationship between maternal inhalation of micro particles (with a diameter of less than 10 or 2.5 microns) and low birth weight in babies born at term and intrauterine growth retardation [43, 44]. Carbon monoxide [45, 46], sulphurdioxide [47] and polycyclic aromatic hydrocarbons [48], all of which contribute to air pollution, may also cause low birth weight and intrauterine growth retardation.

### Developmental toxicity

Developing brain is a target organ for environmental toxic agents. Similar to other organs, brain goes through a series of programmed and scheduled developmental processes during intrauterine life such as cell proliferation, migration, cell differentiation, axon formation, gliogenesis, synaptogenesis, apoptosis, and myelination. Under normal conditions, all these developmental changes occur in a perfectly concerted manner at different sites and pre-determined timeframes within the brain along with the involvement of neurotransmitters (acetylcholine, norepinephrine, dopamine, serotonin, gamma-amino butyric acid/GABA, glutamate, aspartate), hormones (mainly thyroid hormones, steroid hormones, growth hormones, sex hormones), neurotrophins, growth factors, and cellular receptors in the process [49]. Prenatal exposure to methyl mercury interferes with neurogenesis [50], with an eventual disruption of neural migration as well. Ethanol [51] and methyl mercury [52], two developmental neurotoxic agents, have been shown to adversely affect both of the two abovementioned processes, resulting in disrupted cellular differentiation. A similar effect is seen in the case of ethanol, methyl mercury, nicotine, and lead during intrauterine cerebral growth. Synaptogenesis (formation of synapses) is disturbed by ethanol, lead, methyl mercury, parathion, diisopropyl fluorophosphates and polychlorobiphenyls [49]. Exposure to ethanol, methyl mercury, lead and chlorpyrifos may lead to untoward increases or decreases in the cell number in certain areas of the central nervous system via the disruption of neurotropic signals regulating apoptosis. Similar changes may also occur in certain neurodegenerative diseases (Alzheimer's, Parkinson's disease) that occur in later stages of life and can be associated with early progressive neuronal loss and functional deterioration [49].

Structural anomalies caused by exposure to toxic chemicals at the time of intrauterine brain development may not manifest themselves until

the time when normal functions of the area are expected to occur. Thus, it is now obvious that such effects on prenatal cerebral development may lead to neurologic pathologies at distant timepoints during the life course [49]. Epidemiologic data suggest the occurrence of late neurotoxicity with methyl mercury exposure in humans and animals. The most frequent manifestations include motor anomalies and auditory/visual and somatosensory disturbances. Exposure to methyl mercury during a time period from intrauterine life to adolescence has been found to induce disturbed fine motor skills in primates [53].

Aging is associated with decreased cell number, neurotransmitter activity, and repair capacity in certain areas of the brain. Previous chronic exposure to neurotoxins may hasten this process, resulting premature occurrence of the effects of aging. Early exposure to neurotoxins reduces the reserve capacity (plasticity) of brain, again contributing to the emergence of functional disturbances. [53].

Maternal thyroid hormones and thyroid hormones produced by the fetus itself after the 10<sup>th</sup> week of the pregnancy play a critical role in the intrauterine brain development in terms of the proliferation and migration of neurons and glial cells, and in terms of the maturation of dopaminergic and cholinergic systems. They also affect hearing and motor control [54]. Fetal exposure to endocrine disruptors may cause derangements in the thyroid and/or pituitary systems. Herbicides such as 2,4-D and some PCB congeners are known to prevent iodine uptake, and aminotriazole (a herbicide), endosulfan (an insecticide), malathion, and polychlorinated biphenyls prevent peroxidation at molecular level. Some of the endocrine disrupting chemicals interfere with the protein carrier responsible for the cellular iodine intake, and others (PCBs, herbicides such as aminotriazole and dimethoate, and the insecticide fenvalerate) block the release of thyroid hormones from the cell or conversion of T4 to T3 [54].

Maternal PCB exposure leads to the production of hydroxylated PCB metabolites by the maternal hepatic metabolism during normal enzymatic detoxification. However these hydroxylated PCB metabolites exhibit high affinity for an important thyroid transport protein referred to as transthyretin (TTR). Hydroxylated PCB's replace free T4, bind to protein and reach the fetal brain via placental route. Thus, fT4, which is supposed to reach brain and converted to free T3, is superseded by PCB's [55]. Prenatal exposure to organochlorine pesticides have been shown to affect newborn TSH levels [56]. A slight decrease in the circulating maternal free thyroid hormones during pregnancy has been associated with reduction of IQ,

attention, language and reading skills, and general school performance between ages 7 and 9 [57]. Similarly, the incidence of thyroid abnormality in children with ADHD (Attention Deficit Hyperactivity Disorder) is five fold higher [58].

## Lead

Fetal exposure to lead occurs via placenta, which has been shown to provide only a weak filtering effect for lead in a number of studies [59]. Lead that has accumulated in maternal body before pregnancy or exposed during pregnancy may be released in conjunction with calcium due to increased bone turnover during pregnancy and may transferred to fetus via trans-placental route [60]. The transport of lead from maternal bone structures to fetus has been demonstrated by Franklin et al. [61] who found that 7 to 39 percent of the maternal burden of lead in osseous tissues is transferred to fetus. Increased bone resorption due to increased calcium needs during lactation is associated with release of lead from the skeleton leading to detectable levels of lead in the breast milk. Increased maternal age also is associated with higher amounts of lead transferred to fetus possibly due to increased maternal accumulation by age [62].

Although lead may virtually affect any system in the body including hematopoietic, urinary, and reproductive systems, its primary target during fetal development is central nervous system. Lead is an endocrine disrupter that disturbs the production, release, transport, binding and excretion of hormones and is associated with early birth, low birth weight, still birth, and abortion due to its prenatal effects [63]. In a study involving 5,183 subjects, cord blood concentrations of lead correlated with the incidence of some minor abnormalities such as hemangioma, lymphangioma, hydrocele, skin disorders, and undescended testicle. However a similar association could not be shown for multiple or major abnormalities [64].

Intrauterine exposure to lead adversely affects cellular proliferation and differentiation, synaptic growth, and apoptosis at the time of brain development and causes decreased levels of certain neurotransmitters such as acetylcholine, dopamine, and glutamate. Also glutamate receptors are inhibited and density of dopamine receptors is decreased. Fetal exposure to lead may also result in mental retardation, movement disorders, and renal dysfunction [65, 66].

Mice exposed to lead starting from the intrauterine period showed signs of retarded sexual maturation [67]. Also, perinatal exposure in humans was associated with low IQ, decreased performance in skill tests, low

school performance, behavioral changes (dependence, impulsivity, emotional instability, antisocial behavior, offensive and aggressive behavior) and growth retardation at later stages of life [68]. Another observed effect of intrauterine lead exposure in children later in life is decreased performance in specific cognitive tests [69] such as retardation in the gathering process of basic information and attention deficit. In the scientific and medical community, behavioral changes associated with lead exposure during early developmental stages are generally considered irreversible with lifelong effects. [49]. Animal studies also suggest a carcinogenic effect for lead, mainly in the form of renal tumors. Perinatal exposure to lead in mice had carcinogenic effects [70]. Lead has been categorized as a Group B2 agent (probable human carcinogen) by the Environmental Protection Agency in the US on the basis of sufficient evidence from animal studies but insufficient evidence from human studies [71].

## Mercury

Inorganic mercury spills into water resources due to industrial activities and is converted into organic methyl mercury by planktons, which are consumed by simple organisms for nutrition. Through food chain, methyl mercury transferred from larvae to smaller fish and ultimately to larger fish, with increasing accumulation of organic mercury in their fat tissue (bio magnification). The most frequent route of ingestion is through consumption of fish from areas with high contamination. In some countries where fish is a major source of food (e.g. Sweden, Peru, Alaska, and Northern Canada) significant increases in blood mercury levels were detected [72]. Also widespread use of fish as an ingredient in industrial animal food may lead to transfer of mercury to eggs, milk, meat, and farm fish [73]. High consumption of fish also associated with increased hair levels of mercury in mothers [74].

All mercury compounds readily pass placenta and blood-brain barrier. Elementary mercury and methyl mercury may also demonstrate high placental transfer. Similar to lead, primary toxicity of mercury takes place at brain. Low dose exposure to mercury during intrauterine life has been reported to be associated with attention disorder, learning difficulties, memory problems, speech and motor disorders, and problems related with growth and development [75, 76]. In an epidemiologic study from the Faroe Island in the North Atlantic where fish consumption is high (average maternal hair methyl mercury level 4.3 µg/g), an epidemiologic study involving approximately

1,000 births [77] showed an association between high mercury levels in the cord blood and diminished neurologic functions in newborns 2 weeks after birth. In children with a maternal hair mercury level between 15 and 30 µg/l abnormalities in language, attention and memory were detected at age 7, showing the association between intrauterine methyl mercury exposure and such late effects [75]. In the US, the allowance for methyl mercury levels in the cord blood and maternal hair is below 58 µg/l 11 µg/g, respectively. In another cohort study with lower average maternal hair mercury levels (1.6 µg/g), no change in neuropsychological scores were observed between 15 and 18 months of age [78]. In the study from Faroe Islands, alterations in brainstem evoked potentials found at the age 7 and 14 are considered as an indication for irreversibility of neurotoxicity induced by intrauterine methyl mercury exposure. Similarly, decreased heart rate, a marker for autonomic nervous system dysfunction, detected at the same age groups [79]. In conclusion, the study from Faroe Islands has established low dose prenatal methyl mercury exposure due to high maternal fish and whale consumption as an important neurologic risk factor for behavioral developmental disorders in infants and children. In 1953, large amounts of methyl mercury chloride leakage into the Minamata Bay resulted in methyl mercury poisoning in many sites of Japan, particularly in Minamata and Niigata. More than 21,000 people were affected with approximately 600 deaths. Excessive accumulation of methyl mercury in fish and prawn resulted high number of poisoning in those consuming contaminated food. Another incidence of mass poisoning with methyl mercury occurred in Iraq between 1971 and 1972 due to consumed grain seeds treated with fungicides containing mercury. The total number of hospitalizations exceeded 6,500, with 459 deaths. Approximately 50,000 people were exposed to mercury [80]. Both of these tragedies were associated with a number of abnormalities including mental retardation, cerebral palsy, epilepsy, motor weakness, gait disorder, blindness, deafness, and dysarthria in children exposed to mercury during intrauterine life [80-82].

## Cadmium

The major source of cadmium toxicity during pregnancy is cigarette smoking [83]. Mice exposed to cadmium during pregnancy and lactation had 2.5 times higher intestinal absorption of cadmium in comparison with control animals [84]. Maternal bioaccumulation of cadmium may start at an early age and persist for

many years, ultimately passing from mother to fetus through placenta [85]. Fetal harm caused by cadmium may occur via its interference with the metabolism of elements such as zinc, copper, iron, and selenium [86]. Human placenta is vulnerable to cadmium toxicity, and placental accumulation may cause structural and functional changes in the placenta [83, 87]. In animal studies cadmium exposure before or during the pregnancy showed teratogenicity and developmental effects such as low birth weight, sironemelia (fusion of the lower extremities), amelia (absence of one or more extremities), delayed ossification of sternum and costa, facial osseous dysplasia, and behavioral changes [85]. However studies on effects of intrauterine exposure to cadmium in humans are limited. In one study, low birth weight was found in infants whose mothers were exposed to cadmium [88], which is similar to another study from Russia [89]. However other factors that could affect birth weight were not controlled in these two studies. Smoking during pregnancy associated with increased placental cadmium levels which resulted in low birth weight [90]. Cadmium exposure from any source may also lead to exposure in newborns through colostrum [85].

### **Polychlorinated biphenyls**

Toxic effects of PCBs on neurodevelopment first recognized with high number of accidental cases of poisoning in two cities from Japan (Yusho, 1968) and Taiwan (Yucheng, 1979). Offspring's of parents with consumption of contaminated rice oil showed signs of toxicity such as intrauterine growth retardation, brownish skin pigmentation, liver function abnormality, abnormalities of teeth and gingiva. In later stages of the development manifestations included low body weight and height, low IQ, and behavioral problems. The contaminated rice oil contained polychlorinated dibenzofurans.

Chemicals in the PCB family have endocrine disrupting effects with estrogenic and anti-thyroid activity. Intrauterine exposure to PCB lowers thyroid hormone levels in serum [91], which are very important for the proliferation and differentiation of neurons. In a study from the US, cognitive function assessed in children whose mothers, during pregnancy, consumed fish from the Michigan Lake contaminated with PCB. A high level of intrauterine PCB exposure was associated with lower IQ (by 6.1 points on average), two-fold increased risk of having a delay in reading skills (a delay of 2 years on average), and increased risk of speech and attention disorders at the age of 11 [92].

An MRI study in children (mean age: 7.8 years) with prenatal PCB exposure showed that high cord blood PCB levels associated with reduced volume/size of splenium of the corpus callosum (an anatomic bridge between the left and right parts of corpus callosum). Also in the same study, children exhibited certain signs typical of ADHD, such as response inhibition, reduced environmental adaptation capacity, and inability to calm at the age of 4.5 [93].

### **Pesticides**

Although acute effects of pesticides are well known, the data on their chronic effects is limited. Most of the pesticides occupy estrogen receptors with an eventual endocrine disrupting effect. Some studies found an association between cryptorchidism and occupational exposure in the father [94, 95]. In another epidemiologic study, serum DDT/DDE and hexachlorobenzene levels in the mother correlated with the risk of cryptorchidism [96]. Also prenatal maternal serum DDE levels were associated with accessory nipple formation in male newborns [97]. In a cohort study involving Norwegian farmers, pesticide exposure in parents were associated with urinary system abnormalities [95]. Similarly a higher incidence of childhood neoplasias was detected in a group of children from the US whose fathers were licensed pesticide operators, with increased risk when no gloves were used [98].

### **Conclusion**

Fetal environmental toxic chemical exposure and adverse pregnancy and childhood health outcome relationships supported by limited epidemiologic evidence. The possible connection between fetal toxic environmental exposures and increase in some childhood diseases and disorders such as some childhood malignancies (ALL), neuro-developmental disorders and learning difficulties (ADHD, reduced memory and attention, decreased verbal ability, impaired information processing, reduced psychomotor development, adverse behavioral and emotional effects, decreased sustained activity, increased depressed behavior and other endocrine and sexual developmental disorders is an emerging area of concern.

### **Declaration of interest**

No conflicts of interest exist.

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