

Endocrine disrupting compounds in the baby's world - a harmful environment to the health of babies

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Abstract

Globally, there has been a significant increase in awareness of the adverse effects of chemicals with known or suspected endocrine-acting properties on human health. Human exposure to endocrine disrupting compounds (EDCs) mainly occurs by ingestion and to some extent by inhalation and dermal uptake. Although it is difficult to assess the full impact of human exposure to EDCs, it is well known that timing of exposure is of importance and therefore infants are more vulnerable to EDCs and are at greater risk compared to adults. In this regard, infant safety and assessment of associations between prenatal exposure to EDCs and growth during infancy and childhood has been received considerable attention in the last years. Hence, the purpose of this review is to provide a current update on the evidence from biomonitoring studies on the exposure of infants to EDCs and a comprehensive view of the uptake, the mechanisms of action and biotransformation in baby/human body. Analytical methods used and concentration levels of EDCs in different biological matrices (e.g., placenta, cord plasma, amniotic fluid, breast milk, urine, and blood of pregnant women) are also discussed. Finally, key issues and recommendations were provided to avoid hazardous exposure to these chemicals, taking into account family and lifestyle factors related to this exposure.

Keywords: Endocrine disrupting compounds; Infant; Harmful environment; Biomonitoring; Education

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1. Introduction

The environment in which children grow is a very important factor influencing their development. Parents try to take care of every detail, already at the stage of fetal development of their children. However, they are not always aware of the threats that affect the development of the fetus or child. One such threats is environmental pollution, which can affect every stage of human development.

Nowadays, knowledge of the potential effects of environmental exposure on human health is alarmingly basic, which limits our ability to prevent the diseases that these exposures can cause. Undoubtedly, it is also important to raise public awareness of the impact of environmental exposure to diseases, especially among pregnant women.

Endocrine disrupting compounds (EDCs) are one of the most important groups of pollutants which are present in many areas and materials of common life. The exposure to EDCs can occur from products to personal care, from air and food, this is why fetus and children contact with this class of compounds is inevitable. EDCs are thousands of exogenous chemicals or a mixture of chemicals and they are characterized by high ability to mimic or interfere with the endocrine system and metabolism, causing side effects on health (Predieri et al., 2022). Due to the fact that EDCs mostly interpose with metabolic and endocrine pathways during very sensitive periods of human development and grow, the knowledge on several aspects connected with this group of compounds is of great importance. Nowadays, the research is going around the areas: i) pathogenic mechanisms of action of EDCs from wildlife to humans; ii) EDCs impact on health from pregnancy to adulthood; iii) methods of analysis and monitoring of EDCs in environmental, food, biological and other samples.

Three ways of EDCs uptake are known: inhalation, ingestion, and dermal contact (Ercan and Tarcin, 2022). It has been documented that some EDCs are not metabolized and remain in high levels in the environment for a long time and can be found in human and animal bodies after many years of their uptake. Other types can change into substances that are even more toxic can be detected at distances from where they were produced or released.

Many women are unaware that exposure to EDCs during pregnancy often has a significant impact on the developing fetus, which can lead to long-term postpartum pathologies. The government should

educate citizens that EDCs are commonly found in daily personal care products and plastic materials, and compounds such as phthalates, parabens and bisphenols are continuously detected in human blood at high levels (Bradman and Whyatt, 2005; Koutaki et al., 2022; Lundqvist et al., 2006; Ramadan et al., 2020; Wang et al., 2019). As a result, women may be exposed to mixtures of over 50 different EDCs during pregnancy. The incidence of pregnancy complications (e.g., hypertension, postpartum haemorrhage) has steadily increased over the past few decades. Many scientists explain this phenomenon that environmental exposure is one of the potential contributors to this problem. Organic pollutants present in the human body follow the lipid status and are transferred to the fetus during pregnancy and to infants through breast milk. Moreover, EDCs are often found in products intended for babies and children of early stage life, such as diapers, pacifiers, bottles and toys (Arbuckle, 2010; Encarnação et al., 2019; Oliveira Souza et al., 2022; Szczepańska et al., 2016; Turbeville and Sasser, 2020; Wittassek et al., 2009). The authors of guides for pregnant women should also pay attention to this problem and address the issue of environmental exposure, especially in the prenatal period and early childhood, and emphasize the fact that environmental exposure may be responsible for many adverse changes in the body.

It is well known that changes that appear in the early years of life can impact on the way for disease in later stages of life (Ercan and Tarcin, 2022). There is a saying that illustrates this point well, namely "the fetal basis of adult disease". This term is used to depict observations of the maternal, fetal and external environment and identifies an individual's propensity to develop a disorder later in life (Ercan and Tarcin, 2022). Thus, the developmental age at which exhibition to an EDCs occurs is critical, and the information about the uptake, mechanisms of action and biotransformation in baby/human body as well as the monitoring of child environment from the initial days of life are of high importance. This review summarizes these aspects. The main routes of EDCs uptake are described together with specific examples, while the mechanisms of action of EDCs are depicted in very detailed way. The EDCs metabolism as well as the effects of prenatal and early postnatal exposure (up to 3 years of age) on the development of children are also considered. Examples of goods that are used by babies and children together, which contain specific EDCs are also pointed out along with analytical methods which allow to determine these compounds. As it is extremely important to conduct biomonitoring of infants and

children in early stage of life, the methods used for such purposes are also mentioned with literature examples. The Scopus database was used for the literature search with the application of following keywords: endocrine disrupting compounds, infant, biomonitoring of EDC, biological samples (urine, saliva, blood, breast milk) harmful environment, separation methods of EDC, metabolism of EDC (accessed in January 2023). The publications mainly appeared during the last two decades were considered.

As the motivation for this work was to make a complete awareness review of the dangers of EDCs exposure from an early stage of human development, this work was punctuated with advice on how to minimize the delivery of EDCs to the child's body. We believe that this review will be very useful for future readers, not only the researchers who will search for analytical methods, but also the parents who take care their infants and children.

2. EDCs: uptake, mechanisms of action and biotransformation in baby/human body

Due to widespread distribution of EDCs, humans are continuously exposed through multiple sources like polluted environment (water and air), food, consumer products, medications, and many others. However, scientific information regarding the long-term effects of chronic, low-dose exposure to complex mixtures of these chemicals is very limited. Furthermore, little is known about the quantities in which EDCs are taken up and stored in the body.

2.1. Uptake of EDCs

The main route of EDCs uptake depends on the type of chemical and its use. In turn, the fate of EDCs in the human body depends on the properties of the substance, especially its lipophilicity, and thus the susceptibility to bioaccumulation. Most EDCs are lipophilic and bioaccumulate in the adipose tissue, thus they have a very long half-life in the human body and cause a prolonged exposure to these pollutants. A particular example is DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)-ethane) and its metabolites banned for use in the 1970s and still detected in environment and humans. Some EDCs do

not bioaccumulate in the body, an example is bisphenol A (BPA) which has an estimated half-life of approximately 6 hours (Chapin et al., 2008). Nevertheless, it is very often detected in populations (in 93% of people over 6 years of age), like other plasticizers, mostly due to continuous exposure to these chemicals on a daily basis (Yilmaz et al., 2020).

Human exposure to EDCs mainly occurs by ingestion and to some extent by inhalation and dermal uptake (Yilmaz et al., 2020). Food constitutes the main source of EDCs for humans (Mantovani, 2016). Introduced into the environment, EDCs easily bioaccumulate in organisms and contaminate fish, meat, dairy products and poultry products, and from these sources they eventually get into the human body as a dietary component (Sangeetha et al., 2021; Street et al., 2018). Another source of EDCs, however not very significant, is food of plant origin (fruit and vegetable), which is contaminated by plant protection products used in agriculture, e.g. pesticides (Mantovani, 2016). Some EDCs are synthetic components of food products like food coloring additives, while others migrate into food from packaging containing metals, bisphenol A, or phthalates (Amir et al., 2021).

EDCs can be found in a variety of everyday products and goods. A release from consumer products, such as textiles, polishing and cleaning products, cosmetics, and food contact materials is another important route of exposure. In this case, EDCs can enter the human body by ingestion, inhalation, and through the skin.

Inhalation may be a very important route of exposure, especially for some volatile chemicals and semi-volatile compounds (Carpenter, 2006; Coughlin, 1998; Net et al., 2015). Indoor area is an important environment for potential exposure to air-borne chemicals and particles (Hwang et al., 2008).

As fat-soluble substances, EDCs can be transferred to human body through dermal absorption (Carpenter, 2006). Exposure to indoor organic chemicals through the dermal route accounts for only a small percentage of the total exposure, but can be significant (Coughlin, 1998). The risk of transdermal exposure to EDCs concerns also personal care products and cosmetics.

Occupational exposure to EDCs is also a significant route of contamination for people working at risky environment (Coughlin, 1998).

Of special concern is the exposure of pregnant women and infants as the risk of lifelong adverse health effects is enhanced when periods of EDC exposure coincide with the formation and differentiation of organ systems in early development (WHO, 2013).

EDCs may increase the risk of childhood diseases by disrupting hormonally mediated processes critical for growth and proper development during gestation, infancy, or childhood. For example, normal levels of thyroid hormones are of special importance in fetal development, as they condition the proper development of the brain and nervous system. During the first part of pregnancy, the fetus relies entirely on transplacental transfer of maternal thyroid hormones and thus on a normal maternal thyroid function. Thus, even minor changes in the thyroid homeostasis may affect fetal neurological development. Epidemiological studies have indicated that even a marginally low thyroxine level in a pregnant woman may give rise to reduction of cognitive functions of the offspring. Absence of thyroid hormones reduces neuronal growth and differentiation in the cerebral cortex, hippocampus, and cerebellum (Boas et al., 2012).

Development is also a particularly sensitive window of exposure due to the extensive genetic programming that occurs in this time period. Exposures during periods of development can alter the epigenome and increase susceptibility to disease later in life, after the exposure has ended. It has been suggested that exposures in utero and during early postnatal life can make a high impact, not only on development but also on the risk of disease much later in life. This might be the case for cancer, obesity, the metabolic syndrome, diabetes, cardiovascular disease, neurodegenerative disease such as Alzheimer and Parkinson, and mental retardation. Prenatal exposures might even contribute to psychoses (De Coster and Van Larebeke, 2012).

The fetus, infant, and child may have higher exposure and enhanced sensitivity to some EDCs than adults because of specific baby food they consume, behavior (hand-to-mouth activity, crawling), physiology (higher ventilation rates, intestinal absorption, surface area to volume ratios), anatomy, and toxicokinetics (Braun, 2017). In addition, breastfed infants may have higher serum concentrations of some persistent EDCs than their mothers because of lactational exposure (Grandjean and Jensen, 2004). Differences in toxicokinetics can result in higher circulating or tissue concentrations of an EDC for a

given dose. One of the important reasons may be that the fetus, compared to adults, has lower levels of several cytochrome P450 enzymes that metabolize environmental chemicals including EDCs (Creteil, 1998; Hakkola et al., 1998).

2.2. Mechanisms of action of EDCs in baby/human body

Recent epidemiological studies suggest a link between increasing exposure to EDCs and the development of certain civilization diseases such as reproductive disorders, hormone-related cancers, metabolic disorders such as obesity and type 2 diabetes (Guarnotta et al., 2022). Therefore, understanding of molecular mechanisms underlying the physiological consequences of chronic exposure to environmentally relevant concentrations of EDCs is very important.

Endocrine signaling occurs along axes that connect the central nervous system with the target organ. In mammals, the endocrine signaling pathway usually starts at the hypothalamus by secretion of neurohormones. The release of neurohormones upon stimulation of the hypothalamus regulates secretion of the secondary hormone signal by the pituitary gland which in turn control excretion of tertiary hormones by the relevant endocrine gland followed by stimulation of gene transcription in the target organs. The endocrine system controls all the most important physiological functions of the human body. EDCs can affect this complex communication system in a wide variety of ways, disrupt the hormonal balance and cause adverse health effects.

The endocrine system is composed of glands that secrete chemical messengers (hormones) that interact with specific targets (receptors). Different nuclear hormone receptors (NRs) mediate the biological actions of estrogens, androgens, progestins, thyroid hormones, retinoids, and other lipophilic hormones and as a consequence regulate various physiological functions e.g., growth, development, reproduction, immunity, energy balance, metabolism regulation in human.

EDCs were thought to act primarily through NRs mainly steroid hormone receptors (estrogen receptors (ERs), androgen receptor (AR), progesterone receptors (PRs)) (Hall and Korach, 2021), thyroid receptors (TRs) (Brent, 2012) and peroxisome proliferator activated receptor (PPAR) (Sugden and Holness, 2008). Direct binding to hormone receptors is the most studied and best known so far

mechanism of endocrine disruption. Many EDCs have similar structures to NR ligands and can directly bind to these receptors, induce conformational changes in their tertiary structure thus can act as agonists and induce gene expression or as antagonists and inhibit the activity of the receptor (**Table 1**). It is also not uncommon for EDC to display receptor-selective actions; e.g. BPA is an agonist of ERs, but functions as an antagonist of AR (Teng et al., 2013).

Table 1. EDCs known to interact with receptors

Chemical class	Receptor and mode of action	References
Pesticides	AhR agonist/ antagonist	(Warner et al., 2020)
	TR agonist/ antagonist	(Takeuchi et al., 2006)
	PPAR agonist	
DDT and metabolites (DDE, DDD)	ER agonist	(Kuiper et al., 1998)
	AR antagonist	(Kojima et al., 2004)
Phenolic compounds BPA	ER agonist	(Kuiper et al., 1998)
	AR antagonist	(Fang et al., 2003)
	TR agonist	(Kitamura et al., 2005)
PCBs	TR antagonist	(Moriyama et al., 2002)
	ER agonist	(Takeuchi et al., 2011)
	AR agonist/antagonist	(Takeuchi et al., 2011),
polybrominated diphenyl ethers (PBDEs)	TR agonist/antagonist	(Ghassabian and Trasande, 2018), (Zoeller, 2007)
	ER agonist/antagonist	(Hamers et al., 2006)
	AR antagonist	(Hamers et al., 2006)
	TR	(Ghassabian and Trasande, 2018), (Zoeller, 2007)

Phthalates	ER agonist	(Harris et al., 1997)
	ER agonist/antagonist	(Takeuchi et al., 2005)
	AR antagonist	(Lee and Koo, 2007)
PFAS	ER agonist	(Kjeldsen and Bonefeld-Jørgensen, 2013)
Perfluorooctanesulfonic acid (PFOS)	PPAR agonist	(Behr et al., 2020)
Perfluorooctanoic acid (PFOA)		

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249 In addition, EDCs can affect the endocrine system by activating other signaling pathways, in particular
250 that of aryl hydrocarbon receptor (AhR); a key regulator of the cellular response to xenobiotic exposure.
251 AhR is strongly activated by organic compounds such as polychlorinated dibenzodioxins (referred to as
252 dioxin), polychlorinated dibenzofurans (PCDF), polychlorinated biphenyls (PCBs) as well as polycyclic
253 aromatic hydrocarbons (PAHs) like 3-methylcholanthrene (3-MC), benzo[a]pyrene (BaP) and
254 benzoflavone (Swedenborg et al., 2009).

255 The cross-talk between the NR and AhR pathways can also lead to endocrine disruptions. There are
256 several possible mechanisms that have been proposed for interactions between NR and AhR signaling.
257 It has been observed that by interactions with DNA sequences close to NR binding sites AhR can
258 modulate (inhibit or activate) transcription of respective gene. Competition between NR and AhR for
259 common transcriptional co-activators is another mechanism by which AhR ligands may disturb steroid
260 hormone signaling (Swedenborg et al., 2009). It has been shown that also competition between ER and
261 AhR for ARNT is at least partly responsible for the anti-estrogenic properties of the dioxin TCDD
262 (Rüegg et al., 2008).

263 Beside their interference with the genomic pathways, EDCs also exhibit non-genomic mechanisms of
264 action through interactions with membrane-associated NRs and/or G protein-coupled estrogen receptor
265 (GPER/GPR30) (Balaguer et al., 2019). Membrane activation of GPER was shown to rapidly promote
266 intracellular calcium mobilization, cAMP synthesis and to induce a phosphorylation cascade in
267 particular involving ERK1/2, PKA, and PI3K kinases. On the other hand, chromatin binding of GPER

leads to direct transcriptional activation of target genes. Moreover, GPER cross-talk with different receptors induces its downstream activities. For instance, functional interactions with (AhR) or epidermal growth factor receptor (EGFR) and subsequent activation of downstream MAPK kinase were observed (Périan and Vanacker, 2020). EDCs can also influence cell function by targeting membrane associated ion-channels to mediate rapid non-genomic responses (e.g. activation of MAPK signaling) (Warner et al., 2020). Membrane receptor signaling potentially leads to a short-term effect, since their signaling pathways exert more acute effects in target cells. Such mechanism of action was described for the plasticizer DEHP (bis-2-ethylhexyl phthalate), classified as an endocrine disruptor and also as an obesogen (Schaedlich et al., 2018). Interestingly, it has been shown that bisphenol-A exhibits a higher affinity towards GPER than towards nuclear ER receptors (Kerdivel et al., 2013).

According to the classical, ligand-dependent, molecular mechanism of action, hormones are transported through the circulatory system to reach their target intracellular receptors. The binding of a hormone to receptor triggers specific intracellular responses. Therefore, the availability of hormones determines the proper functioning of the endocrine system and all hormone-dependent processes in the body. Hormone availability to receptor is dependent on hormone biosynthesis, transport to the target tissue, levels of hormone binding proteins, and hormone catabolism. EDCs have been described to interfere with all of these processes.

Many molecules can exert endocrine disruption by affecting, positively or negatively, endogenous hormone biosynthesis or degradation. Such molecules generally exhibit structures that are different from those of hormones, since they do not compete with hormones at the receptor level. It has been shown that exposure to EDCs can negatively affect the synthesis and degradation of peptide/protein (gonadotropin-releasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH)), steroid (estrogens, progesterone, and testosterone), and amino acid analogue (thyroid hormones (T4, T3)) hormones (Warner et al., 2020). Interfering with hormone quantity and availability may cause negative effects on reproductive and overall human health. Epidemiological studies of agricultural workers showed associations between pesticide exposure and levels of FSH and LH (Cremonese et al., 2017; Recio et al., 2005). Exposure to EDCs disturbs the

process of steroidogenesis (synthesis of steroid hormones) that occurs in adrenal glands, ovary, testes, placenta, and adipose tissue. Multiple chemicals have been shown to affect the synthesis of cholesterol, which is precursor for all steroid hormones, as well as enzymes involved in the synthesis and conversion of steroid hormones. Inhibition of 17 β -hydroxysteroid dehydrogenase (17 β -HSD; an enzyme that converts estradiol to estrone) was observed after exposure to parabens and resulted in an increase in estrogen concentrations and consequently, in an increase of the transcription of target estrogen genes (Engeli et al., 2017). EDCs often act as inhibitors of 5 α -reductase, which is necessary for conversion of androgens (activation of testosterone to dihydrotestosterone (DHT)) essential for the development of the male genital tract (Jeřeta et al., 2021; Sweeney et al., 2015). EDCs can also influence TH signaling at the level of gene expression and regulation of enzymatic activity of iodothyronine deiodinases (DIO). In the target tissues, three DIO (DIO1, DIO2, and DIO3) are involved in regulation of thyroid hormone (T4 (prohormone thyroxine) and T3 (triiodothyronine)) levels. DIO2 catalyzes the conversion of T4 to biologically active T3 whereas DIO1 and DIO3 metabolize both T4 (converted firstly to inactive T3 (rT3)) and T3, thereby diminishing TH signaling (Brent, 2012). Decreased gene expression of deiodinases and thyroid hormone homeostasis imbalance were reported after exposure to glyphosate-based herbicide (Sena et al., 2017). Iodine is crucial for thyroid hormone synthesis and is entrapped into thyrocytes by the sodium/iodide symporter (NIS) (Brent, 2012). Several environmental chemicals may interfere with NIS function and iodine uptake. It has been shown that DDT down-regulate the iodine-accumulation function of thyrocytes by suppressing NIS synthesis and disrupting regular thyroid function (Yaglova and Yaglov, 2015). Another mechanism by which EDCs may interfere with thyroid function, observed for BPA and also for nonylphenol, is inhibition of thyroperoxidase (TPO), enzyme which is essential for thyroid hormone synthesis (Schmutzler et al., 2004).

Moreover, some EDCs have been described to act through the induction of hepatic enzymes involved in hormone metabolism by sulphation and glucuronidation which potentially lead to a decrease in hormone levels. The decline in T4 hormone level after exposure to polybrominated diphenyl ethers (PBDEs) is believed to be an effect of glucuronidation (Boas et al., 2012). Steroid hormone catabolism is particularly affected by EDCs, since many of the xenobiotic-metabolizing enzymes induced by activated AhR (for example, the P450 enzymes CYP1A2, CYP3A4, CYP1A1, and CYP1B1) are also

involved in the catabolism of e.g., steroid hormones. Thus, induction of these enzymes upon exposure to xenobiotics can lead to reduced availability of endogenous hormones, and consequently, influence hormone signaling. Conversely, recent experiments have shown that CYP19B (aromatase), which converts testosterone to estradiol is a direct AhR target gene. Thus, activation of AhR by EDCs can lead both to increased degradation of steroid hormones as well as to higher estradiol production (Swedenborg et al., 2009).

Many hormones, especially hydrophobic ones (steroids and thyroid hormones), are transported by binding proteins in the blood. A number of EDCs directly interfere with hormone-binding transport proteins and thus affect hormone bioavailability. The chemicals exerting their effect through this mechanism exhibit some structural resemblance with the hormones, so that they can compete with them for binding with hormone-binding transport proteins. For example, numerous chemicals have been shown to interact with SHBG (steroid hormone-binding protein) (Hong et al., 2015; Sheikh et al., 2016) and thus, to interfere with steroid hormone transport and concentration in blood. The major serum TH-binding proteins are thyroxine-binding globulin (TBG) and transthyretin (TTR). EDC binding to these carrier proteins disturb even distribution and delivery of the hormone throughout the body (Boas et al., 2012).

Other EDCs affect the biosynthesis or degradation of hormone-binding transport proteins, so that both the total hormone concentration and/or its free active fraction can be affected. For example, PBDEs act through the down-regulation of the transport protein transthyretin (TTR) (Boas et al., 2012) and therefore can influence T4 concentration in the blood.

At target cells, thyroid hormones are probably actively transported across the cell surface via membrane bound transporters. Recently, MCT8/10, OATP-1c1, and System L amino acid transporters have been reported to be TH transporters that regulate T4 and T3 uptake into cells (Heuer and Visser, 2013). Interference of EDCs with these proteins may compromise the bioavailability of thyroid hormones to the nuclear thyroid hormone receptors.

The abundance of receptors can determine the magnitude of the effect produced and also the concentration of hormones in blood. EDCs can alter hormone receptor synthesis (by inducing/inhibiting

gene synthesis), distribution and degradation. Rebuli et al. (Rebuli et al., 2014) reported changes in the expression of ER gene, and receptor distribution in specific regions of the brain after exposure to BPA and suggested that subchronic, low dose BPA exposure may influence sex-specific brain development. Further, it has been shown that exposure to BPA resulted in reduced proteasome-mediated degradation of ER (Masuyama and Hiramatsu, 2004). EDCs can affect receptor abundance by inducing NR proteasome-dependent degradation with the participation of AhR. Both AhR and its heterodimerization partner (ARNT) are a part of a multi-protein complex involved in targeting proteins to the proteasome. Additionally it has been suggested that AhR ligands can interfere with hormonal signaling by targeting hormone receptors to the proteasome (Swedenborg et al., 2009).

The epigenome, which consists of all chemical and structural marks that control the accessibility of the genome, is highly sensitive to environmental conditions including chemical exposures. Recent studies have shown that EDCs can also alter the epigenome. Three mechanisms of epigenetic modification which change gene availability and expression without changing DNA sequences have been identified; acetylation and methylation of DNA and histones and expression of non-coding RNAs (particularly micro-RNAs (miRNAs) - important regulators of post-transcriptional gene expression) (Singh and Li, 2012). Methylation is generally a silencing mark, which acts by blocking access of transcription factors to genes and DNA methyltransferases (DNMTs) are responsible for DNA methylation and demethylation. It has been shown that BPA, BBP, DEHP and pesticides exert their endocrine disrupting activity by altering methylation patterns. Moreover, EDCs can also affect (induce or inhibit) expression of miRNAs, as has been seen for example for PCBs (Topper et al., 2015), BPA (Amir et al., 2021) and phthalates (Singh and Li, 2012). Changes to the epigenome can be heritable and can manifest impact on health and disease even multiple generations after the exposure occurred (Rattan and Flaws, 2019). For example, vinclozolin and methoxychlor exposure during pregnancy have been shown to decrease fertility in male descendants for up to four generations (Anway et al., 2005). The effects of these chemicals on germ cell genomes make these outcomes heritable.

As described above, EDCs may exhibit many different molecular mechanisms of action. Some of them (such as binding to receptors or hormone transporter proteins) are related to the structural similarity of

chemical compounds to endogenous hormones. Other mechanisms of action, such as inhibition of enzymes related to the synthesis, conversion or degradation of hormones, synthesis or degradation of proteins involved in the transport of hormones or degradation of receptors, are not reserved for compounds with a specific structure. In addition, EDCs with chemical structure similar to endogenous hormones (e.g., BPA similar to estradiol) as well as all EDCs showing a mechanism of action that influence the blood levels of hormones can cause disruptive effects on the feedback regulation of the hypothalamic–pituitary–gonadal/thyroid axis. The results of studies showing that EDCs can influence the epigenome and induce changes, the effects of which can be inherited over many generations are particularly worrying.

2.3. Metabolism of EDCs in human body

The group EDCs is highly heterogeneous and comprises compounds that are very different in terms of size, chemical structure, physicochemical properties, and biotransformation susceptibility. In the human body EDCs are subjected to the two-phase detoxication mechanisms as are other foreign compounds (Reinen and Vermeulen, 2014). Phase I reactions include hydroxylation, hydrolysis, oxidation, and reduction. During these enzymatic reactions, a new functional group is introduced into the molecule, an existing group is modified, or an acceptor site for Phase II reactions is exposed to make the substrate more polar and therefore more readily excreted. The most important enzymes involved in Phase I of metabolism are Cytochromes P450 (CYPs). They are liver microsomal enzymes with monooxygenase activity and are characterized by broad substrate specificity. The multitude of reactions that CYPs can catalyze makes these enzymes highly versatile. Other Phase I biotransformation enzymes are reductases, peroxidases, monoamine oxidases, epoxide hydrolases, oxidoreductases, flavin-containing monooxygenases, xanthine oxidases, dehydrogenases, and carboxylesterases. In Phase II, the parent compound (if it has the appropriate chemical group) or the product of Phase I metabolism is conjugated with a highly water-soluble moiety (e.g. glucuronic acid) to facilitate its removal from the body, usually with bile or urine. In addition to glucuronidation Phase II biotransformation reactions include sulfonation, glutathione and amino acid conjugation, acetylation, and methylation. Key Phase II

enzymes include UDP-dependent glucuronosyl transferases (UGTs), N-acetyl transferases (NATs), sulfotransferase SULTs, and glutathione S-transferases (GSTs), steroid sulfatase (STS) and catechol-O-methyltransferase (COMT) (Jordan and Woolf, 1987; Woolf and Jordan, 1987).

It has been shown that many different enzymes may be involved in the biotransformation of EDCs (Reinen and Vermeulen, 2014). This is not surprising due to the large numbers of EDCs known and their diverse chemical structure. Moreover, EDCs are characterized by different susceptibility to biotransformation. As a result unchanged mother compounds (BPA), phase I metabolites (PHAH-Ohs, monoester phthalates) as well as glucuronide and sulphate conjugates are detected in human urine (Azzouz et al., 2016; Frederiksen et al., 2007; Reinen and Vermeulen, 2014; Sangeetha et al., 2021).

Metabolism/biotransformation does not always mean detoxification; in some cases, as a result a metabolite with greater biological activity is formed. For example, CYPs can bioactivate PAHs into reactive metabolites that react with DNA. Another pathway by which PAHs can be activated is sulfonation (Reinen and Vermeulen, 2014). It has been shown that dibrominated biphenyls are activated by CYP into very potent estrogenic metabolites that similarly to hydroxylated PCB metabolites inhibit human estrogen sulfotransferase activity (Van Lipzig et al., 2005). In vitro and in vivo studies have shown that the monoester phthalate metabolites are more potent EDCs than the diester parent compounds (Sheikh et al., 2016).

2.4. Elimination of EDCs from the human body

The elimination of EDCs from the human body depends on many factors such as nature of chemical compound, the route of exposure, age, and the health condition of the body. EDCs can be eliminated from the infant and children body, depending on the nature of chemical compound, in unchanged form (as a parent compound) or as a product of metabolism. The proportion of parent compound excreted from the body may depend on the route of exposure. For example it was observed that uptake of parabens through the skin resulted in more parent compound excreted in urine compared with oral uptake (Beltifa et al., 2019). Usually, EDCs like parabens, bisphenols and phthalates with half-life times of less than 24 hour considered non-persistent are quickly metabolized and completely excreted from the human body

in urine, feces and sweat (Søeborg et al., 2014). BPA-glucuronide and BPA-sulfate, parabens in native form and their two metabolites (p-hydroxybenzoic acid and p-hydroxyhippuric acid), phthalate monoesters and conjugates are frequently detected in the urine samples. Therefore urine is considered the most appropriate matrix used for biomonitoring and assessment of parabens, bisphenols and phthalates exposure (Geens et al., 2014).

Some EDCs, exemplified by PCBs, OCPs, HCBs, and dioxin, were designed for industrial purposes to have long half-lives and are known as persistent organic pollutants (POPs). The POPs are highly lipophilic and tend to accumulate in the adipose tissue. These persistent EDCs are transferred from mother to infants through breast feeding (Kabir et al., 2015).

Since metabolic and excretion systems in infants are not fully developed, they may suffer from the severe effects of EDCs (EFSA Scientific Committee, 2017).

3. Fetal and early-life exposure to EDCs and its consequence

Since EDCs are common in the environment, bearing in mind their uptake, the mechanism of action and the activity of biotransformation products, it can be expected that their presence will interact with living organisms (Nesan and Kurrasch, 2020). Among humans, the most sensitive to the effects of external factors are human fetuses, infants and children. The reason for this is the fact of their continuous dynamic development, the constant creation of new cells combined with the immaturity of the essential systems in the body. Because of this, any substance that disrupts their function can have a potentially toxic effect. The most studied EDCs with potential long-term human health effects are plastics and plasticizers (bisphenol A and phthalates). BPA is the most commonly produced substance, replaced with bisphenol F (BPF) and bisphenol S (BPS) in some consumer products (Predieri et al., 2022). As summarized in a comprehensive reviews by Ramirez et al. (Ramírez et al., 2022) and Predieri et al. (Predieri et al., 2022) epidemiological studies report that among EDCs with great impact on developmental disorders are also polybrominated flame retardants, pesticides, heavy metals, polychlorinated biphenyls, perfluoroalkyl substances (PFASs) and polycyclic aromatic hydrocarbons. According to the available literature, EDCs show effects on pregnancy and fetal development and long-term effects on the development of the

nervous system, metabolism, maturation process and functioning of the reproductive system. Examples are presented in **Figure 1**.

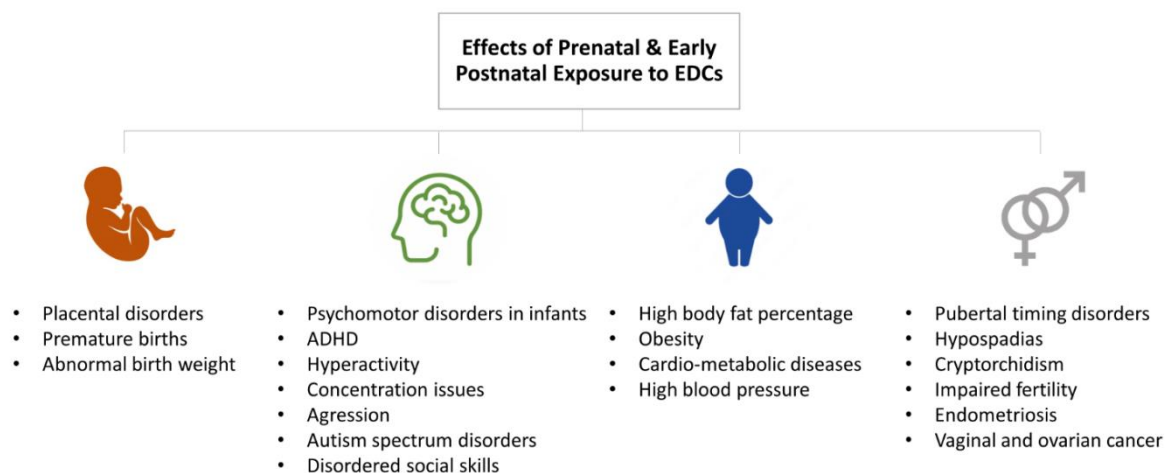


Figure 1. Effects of prenatal and early postnatal exposure (up to 3 years of age) of endocrine disrupting compounds on the development of children

3.1. *Fetal growth and gestation length*

Homeostasis of growth-regulating systems in the uterus can be modified by various factors, increasing the risk of pathological conditions (Gross et al., 2020; Street and Bernasconi, 2020). Maternal intake of adequate nutrients (carbohydrates, lipids, proteins, minerals, vitamins) and oxygen certainly plays a primary role in this process, as evidenced by the altered fetal growth when the intake of these substances is reduced or excessive. Also, maternal diseases (such as infections, diabetes or autoimmune diseases) and/or poor lifestyle habits of the mother (drugs, tobacco, alcohol) or the use of therapeutic drugs can derail fetal growth. Scientists have begun to look more closely at the effects that EDCs, which are widespread in the environment, can have on the health of both the mother (Varshavsky et al., 2020) and the fetus (Di Renzo et al., 2015; Street and Bernasconi, 2020). Two main issues have emerged from the studies of the effects of EDCs. The first is the issue of the EDCs producing effects at doses much lower than those used in traditional toxicology studies conducted to assess chemical risk (Mallozzi et al., 2016). These low doses can produce effects in organisms that are not predicted from effects observed at very high doses. Second, humans show high vulnerability to exposure to EDCs during critical periods

of development (e.g. gestation) (Predieri et al., 2022). According to the available literature, EDC substances affect all stages of pregnancy, from conception to delivery, as well as the health of the newborn (Predieri et al., 2022; Street and Bernasconi, 2020). Moreover, exposure to EDCs during the early life stage can cause epigenetic shifts (besides other effects) on protein content, cell number, cell size, organ size, and function. These changes can be transmitted over several generations as "non-transmissible diseases" (Rager et al., 2020).

Epidemiological studies also reported correlations between *in utero* exposure to major EDCs and birth outcomes. For example, back in 2010, data was published for Mexico showing that women who gave birth before 37 weeks gestation (i.e. classified as premature babies) had significantly more BPA and phthalates in their blood than those women who gave birth on time (Cantonwine et al., 2010; Meeker, 2012). Also, looking at more recent research results, one can see recurring relationships in terms of the effects of EDCs on fetal development and pregnancy in different countries of the world. A large-scale prospective study from 13 European cohorts suggested that exposure to one or more EDCs groups was associated with a higher risk of low birth weight (LBW) in newborns (Street et al., 2018). The risk increased with the increasing number of different EDCs suggesting a possible exposure-response relationship. Conversely, higher concentrations of persistent organic pollutants (POPs) measured in newborn dried blood spots were found to be positively associated with a slightly higher risk of larger than expected size for gestational age and higher birth weight (Bell et al., 2019). Therefore, the problem of the effect of EDCs on fetal development is complex. This is because EDCs also interact with each other, entering into competitive interactions with elements of the endocrine system. Due to this the composition of the EDCs mixture to which the pregnant woman is exposed is also important. The effect of PCBs exposure, for example, may be different from that of a mixture of PCBs and PFAS (Pearce et al., 2021). Combinations exhibiting higher levels of polybrominated diphenyl ethers and p,p'-1,1,1-trichloroo-2,2-bis(4-chlorophenyl)-ethene (p,p'-DDE) were associated with lower birth weight, while combinations with higher levels of PCBs and PFAS were associated with increased birth weight. Also, serum levels of PCBs and p,p'-DDT/DDE were measured in a German cohort of 324 pregnant women (Krönke et al., 2022). In this case neonatal birth length (the size of the baby) was negatively correlated

with elevated levels of maternal PCBs. Positive associations were observed between different levels of maternal PCBs and weight gain at birth.

As mentioned earlier, the effects of BPA and phthalates on pregnancy are also widely reported in the literature. However, there is a lack of a single coherent study on the subject, although a number of diverse papers are available. Combined exposure to BPA from dietary and non-dietary sources during pregnancy may contribute to a trend toward fetal growth restriction (Vrachnis et al., 2021). Also, high levels of BPA in maternal blood, urine or amniotic fluid have been associated with lower neonatal birth weight (Street et al., 2018). Moreover, exposure to unconjugated BPA in the 1st trimester and at the end of pregnancy was associated with a sex-dependent reduction in birth weight. In addition, early BPA exposure was shown to be negatively correlated with intrauterine linear growth. According to Predieri et al. (Predieri et al., 2022) the increase of BPA/creatinine concentration in maternal urine (tested in the 3rd trimester) may be associated with a decrease in femur length. However, in this case an increase of BPA/creatinine concentration was correlated with increased birth weight.

Phthalate exposure during pregnancy may be also associated with increased odds of prematurity. Possible mechanisms are interference with placental function and steroidogenesis (Iughetti et al., 2020). Moreover, phthalates may have trimester-specific and sex-specific effects on fetal growth and birth outcomes. It was demonstrated by Li et al. (Li et al., 2021) (in their all trimesters comprehensive study) that the 1st-trimester urinary DEHP level was negatively related to fetal growth of males, the 2nd-trimester DEHP was negatively related to their birth weight and length, and the 3rd-trimester DEHP was positively associated with birth weight of boys. Among females, the 1st-trimester DEHP was associated with increased birth length.

The pesticides may have some negative effects on fetal growth and gestation length. Pesticide exposure during the 2nd-trimester of pregnancy was negatively associated with weight, length, and head circumference at birth (Gore et al., 2015). However, prenatal exposure to pesticides, like other EDCs, can also affect birth outcomes in a variety of ways, which was confirmed by studies held in Japan and France (Béranger et al., 2020; Matsuki et al., 2020).

Fetuses exposure to PFAS may also lead to decreased birth weight, according to Predieri et al. (Predieri et al., 2022). For example, high concentrations of perfluorooctane sulfonic acid (PFOS) and perfluorohexanesulfate measured in newborn dried blood spots were demonstrated to be related to lower birth weight scores compared to those with low concentrations (Gross et al., 2020). Furthermore, increased concentration of PFOS, perfluorooctanoic acid (PFOA), perfluorononanoic acid, perfluorodecanoic acid, and perfluoroundecanoic acid levels in maternal serum during pregnancy were associated with lower birth weight and SGA at birth (Wikström et al., 2020). However, in this case the associations were significant only in girls.

Also in case of PBDEs studies reported correlations with birth weight. In case of study by Street et al. (Street et al., 2018) the differences between sexes were significant – for the males the correlation was negative, in case of females it was positive. In a study conducted by Yu Ting et al. (Yu Ting et al., 2020) 19 PBDEs were detected in maternal serum samples collected during the third trimester of pregnancy and were negatively associated with placental size and birth outcomes. Concentrations of BDE-207, -208, -209 and total 19 PBDEs were higher in newborns with fetal growth restriction compared to healthy ones.

The presence of EDCs in a pregnant woman's body, and consequently her baby's body, can cause not only pregnancy-related problems, but also long-term effects on the functioning of the nervous system (**Section 3.2.**), immune and metabolic balance (**Section 3.3.**), and reproductive system (**Section 3.4.**). The consequences on the child's development are described in the following sections of this paper.

3.2. *Effects of EDC on childhood neurodevelopment*

Available scientific studies indicate that exposure to EDCs causes severe effects on human nervous system, due to the ability of these compounds to cross placental and blood-brain barriers (Ghassabian and Trasande, 2018; Ramírez et al., 2022). Given that pregnancy and early childhood are the most crucial stages for the proper development and function of the neuroendocrine system, both prenatal and postnatal exposure to EDCs becomes a matter of great concern. Also, puberty may be an important

period of vulnerability to the harmful effects of EDCs due to the high neuroendocrine activity that takes place during this period (Lucaccioni et al., 2020). Exposure to low doses of neurotoxicants during these key developmental periods can lead to permanent brain damage that can affect quality of life, learning ability, memory and neurotic behavior, and increase the risk of adverse effects later in life (Grandjean and Landrigan, 2015; Ramírez et al., 2022). The neurotoxic effects of EDCs depend mainly on the type of disruptor, time of exposure, dose and duration of exposure (Gore et al., 2019; Parent et al., 2011). EDCs can exert their neurotoxic activity through multiple mechanisms. For example, interaction with nuclear hormone receptors such as estrogen receptors, androgen receptors and thyroid receptors, while hypothalamic-pituitary-thyroid (HPT) axis is known to play an essential role in perinatal brain development (Kabir et al., 2015). Therefore, early exposure to TH-disrupting EDCs is thought to be a risk factor for increased incidence of developmental disorders (Ghassabian and Trasande, 2018). Also, exposure to EDCs in general induce changes in the levels, transport and receptors of certain neurotransmitters, including dopamine, serotonin, glutamate and gamma-aminobutyric acid (Nesan and Kurrasch, 2020). Another possible mechanism of action of EDCs would be disruption of the neuroimmune system. For example, mercury species can suppress or activate immune-inflammatory pathways (Morris et al., 2018).

3.2.1. Psychomotor functions of babies

Literature data indicate that exposure of young children to POPs can cause impairments in their psychomotor development (Klocke and Lein, 2020). For example, a few available studies have evaluated the neurotoxic effects of PCB-153 (2,2',4,4',5,5'-hexachlorobiphenyl). With regard to cognitive deficits, exposure to PCB 153 in breast milk was found to result in impaired psychomotor development at 24 months of age (Lynch et al., 2012). Performed study assessed sensory and perceptual abilities, memory, problem solving, learning and early verbal skills. Moreover, the physical activities that require the use of both large (such as sitting and walking) and small motor skills (such as lifting small objects) were taken into consideration. The same test was applied in study by Verner (Verner et al., 2010), where infants and babies between 1 to 11 months old were observed to be more active at 11 months when

583 exposed to PCB-153, which indicates a differentiated mechanism of action of PCBs depending on the
584 interacting environment and possible associated substances.

585 Also, pesticides have been observed to alter children's cognitive development. For example, for 3-
586 months-olds, where the organophosphates and pyrethroid exposure was measured for both pre- and
587 postnatal development phase, postnatal urinary metabolites significantly impacted mental skills of the
588 babies (Fluegge et al., 2016). For children this young, no effect on motor development has been
589 observed. Also in paper by Kao et al. (Kao et al., 2019) it was indicated that levels of DDT and trans-
590 CHL (trans-chlordane) are associated with lowering cognitive abilities, early language and socio-
591 emotional skills in babies between 10 and 12 months of age. Eskenazi et al. (Eskenazi et al., 2007)
592 performed a study, where the effect of total pesticides prenatal and postnatal exposure (to 2 years of
593 age) on the babies neurodevelopment was measured. Prenatal exposure to organophosphates
594 significantly increased the risk of pervasive developmental disorder at 2-year-olds (e.g. autism
595 spectrum disorders), which is in agreement with a review article by Moosa et al. (Moosa et al., 2018).
596 Similar results were obtained by Liu et al. (2016) and by Guo et al. (2019) (Guo et al., 2019)(for 3 year-
597 olds), also covering problems in children's motor development. In most cases a more significant
598 development delay was observed among boys.

599 Also available in the literature are studies indicating that exposure to PBDEs in the pre- and postnatal
600 period is not without effects on the development of psychomotor functions in infants and young children.
601 For example, higher BDE 209 levels in mother's breast milk showed a significant association to lower
602 mental scores in children aged from 8 to 12 months. However, exposure to BDE 196 was positively
603 correlated with verbal development (Chao et al., 2011). Similarly, both in work by Hoffman (Hoffman
604 et al., 2012) and Adgent (Adgent et al., 2014) it is indicated that increased level of total PBDEs in breast
605 milk can positively influence language and motor skills in children at the age of 30-36 months. However,
606 it was also indicated that particular BDEs can still cause severe issues with anxiety, withdrawal
607 behaviors (BDE 99 and 28) and impulsivity (BDE 47).

609 3.2.2. Further neurobehavioral changes

Many of the available research findings also point to possible effects of prenatal and early postnatal EDC exposure on further children's neurobehavioral development. In the case of PCBs, some of the most extensively studied EDCs, consistent relationship was found between attention problems and hyperactivity (Verner et al., 2015). An observation in this study was performed on 2 month-olds to 5-year-olds. The same team performed study on the possible relationship between PCB-153 serum level and the development of disorders like ADHD or impulsive behavior, where both these issues were confirmed (Verner et al., 2015). This study covered 8 years from the lives of children who were exposed to PCBs from fetal life.

With regard to ADHD, a prospective Norwegian cohort study addressed postnatal exposure by determining pesticides hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β -HCH), p,p'-DDT, p,p'-DDE and oxychlordane in breast milk and blood of infants collected two months after birth and during first two years of life (Lenters et al., 2019). From all tested children, 55 of them (4.6%) were diagnosed with ADHD around the age of 14 years old. Interestingly, a strong association of early exposure to β -HCH was found with an increased risk of ADHD, while DDT appeared to decrease the risk. In many of the remaining cases suspected ADHD was noted, but it is not known what diagnoses were made after the described studies were completed. At the same time, the wide pool European study made by Forns et al. (2018) shows no correlation between pre- and postnatal exposure to pesticides and a diagnosis of ADHD. Thus, the effect of pesticides on the incidence of ADHD in children is not clearly defined. According to more general influence of early pesticides exposure to long-term neurodevelopment of children, these compounds have a negative effect on verbal comprehension and working memory, which was observed among group of almost 300 tested children (Viel et al., 2015).

PBDEs pre- and postnatal exposure have also been shown to be associated with decreased ability to concentrate, but also low social skills of 4-year-olds (Gascon et al., 2011). Moreover, Vuong et al. (2019, 2018, 2017a, 2017b) conducted a study on the effects of PBDEs on the development of children of different ages (1, 2, 3, 5 and 8 years old). An increase in BDE 153 at 3 year-olds was significantly associated with increased risk of metacognition dysfunction. Further, toddlers exposure to BDE-153 was associated with decreased concentration and attention in children aged 6 years and older. In

addition, exposure to multiple PBDE congeners was associated with increased hyperactivity and aggressive behavior at age 8. Especially higher BDE 153 and 28 levels were correlated with a significant impairment in behavioral regulation, emotional and impulse control at 8 years of age. Also, differences between sexes were observed, where males showed higher functioning problems with higher BDE 153, compared to females.

There is not much information about the influence of heavy metals early exposure (prenatal and postnatal to 2nd-3rd year of live) and its long-term consequences towards the nervous system. According to a paper by Liu et al. (Liu et al., 2018) increased level of Pb in blood may negatively affect cognitive and language skills of 3-year-olds, whereas there is no correlation with Cd level.

Interesting findings were published in 2020 on the impact of children's prenatal exposure to different EDCs vs. their IQ at age 7 (Tanner et al., 2020). Early prenatal exposure to a mixture of suspected EDCs was related to lower levels of cognitive functioning, particularly among boys. Bisphenol F made the largest contribution to the mixture effect estimate, suggesting that BPA replacement analogues may not be any safer.

3.3. Obesity and metabolism diseases

Obesity is a multifactorial disease caused by a disruption of the balance between the amount of calories consumed and energy used (Casals-Casas and Desvergne, 2011; Predieri et al., 2022). It is largely influenced by genetic predisposition and environmental factors, including EDCs. Studies reported data related to the association between exposure to EDCs during pregnancy and birth weight combined with fast weight gain in early childhood, underlining the risk to develop overweight, obesity and other diseases later in life due to altered “programming” *in utero* (Iughetti et al., 2015). Moreover, metabolic diseases are among the most well-known health effects of human exposure to EDCs (Gutiérrez-Torres et al., 2018). For example, prenatal exposure to low concentrations of EDCs has implications for cardio-metabolic risk factors in preschool children. Also, “obesogens” EDCs are risk factors for type 2 diabetes and certain EDCs may directly cause defects in insulin (INS) production and secretion even without

affecting the weight. Moreover, EDCs can disrupt body glucose homeostasis by affecting both INS- and glucagon-secreting cells (Alonso-Magdalena et al., 2021; Iughetti et al., 2015; Street et al., 2018).

Regarding the impact of specific examples of EDCs on the development of obesity and related diseases, studies suggested that *in utero* exposure to p,p'-DDT, p,p'-DDE, and HCB, may increase the risk for rapid weight gain in infancy and high body mass index (BMI) later in childhood and during puberty (Warner et al., 2017). According to Güil-Oumrait et al. (Güil-Oumrait et al., 2021) HCB exposure was also associated with higher BMI, and weight-to-height ratio and a continuous increase in HCB levels were associated with higher body fat percentage and diseases like systolic and diastolic blood pressure, cardio-metabolic-risk and lipid biomarkers. Also, association between *in utero* POPs exposures and major risk factors for the adult cardio-metabolic syndrome was reported (Güil-Oumrait et al., 2021). Similar observations were made for PFASs, PCBs, propylparabens and pesticides, where prenatal exposure to these EDCs caused increased body weight of the baby in the postnatal phase (Berger et al., 2021; Lauritzen et al., 2018; Marks et al., 2021). However, there are some exceptions, like study by Guo et al. (Guo et al., 2020) where serum levels of BDE-153 and -154 in cord blood have been associated with reduced rates of obesity at seven years of age.

Obesity in children has been reported to be induced by exposure to phthalates during pregnancy. Certain phthalates and their metabolites in maternal urine were strongly associated with BMI scores, waist circumference, percent body fat in children of different ages, low-density lipoprotein cholesterol, triglyceride and glycaemia (Golestanzadeh et al., 2019; Harley et al., 2017). In a population of 12-year-olds, *in utero* levels of the metabolites diethyl phthalate, dibutyl phthalate and DEHP were positively associated with overweight or obesity (Miura et al., 2021). It is stated that differential DNA methylation may link phthalate exposure *in utero* to fetal growth, having a predictive value for child's obesity.

Also *in utero* exposure to POPs seems to determine permanent physiological changes influencing birth weight, pre-disposing to subsequent weight gain. POPs have direct effects on insulin signaling leading to insulin resistance that causes adipose tissue inflammation (Iughetti et al., 2015). Moreover, an association was found between gestational BPA levels and central obesity in early childhood (Braun et al., 2019). Maternal urinary BPA levels were associated with a higher risk of central obesity for the

children, and a positive association of dietary exposure to BPA (Mustieles et al., 2019). BPA exposure during prenatal period was also associated with increased blood pressure in girls and plasma glucose level in boys (Ouyang et al., 2020).

However, referring to the review paper by Predieri et al. (Predieri et al., 2022) it should be noted that not all data on the impact of EDCs on obesity and obesity-related diseases are conclusive. Again, as mentioned in other chapters, the mechanism of effect of EDCs on the child's body before and after birth is complex and must be considered on a case-by-case basis.

3.4. Reproductive health

Fetal and early-life exposure to EDCs may also cause severe issues in reproductive system and further pubertal development (Predieri et al., 2022). These are described in this Section.

3.4.1. Maturation

In utero exposure to some metabolites of phthalates and BPA has been linked to delayed sexual maturation in women, especially those of normal weight, and premature sexual maturation in men, especially those who are overweight/obese, emphasizing that body weight can also interfere with such associations (Berger et al., 2018). This was confirmed by Berman et al. (Berman et al., 2021), who proved that age of menarche was found to be slightly delayed in girls with higher prenatal exposure to phthalate metabolites. Depending on the sum of phthalate metabolites, the age of menarche was found to be significantly later in subjects from the middle tercile of concentrations compared to those from the lowest tercile. There is also limited evidence on the potential impact of PFAS exposure on long-term reproductive health, but gender-specific alterations of pubertal timing with different prenatal exposure to PFASs were suggested (Predieri et al., 2022). Later age of menarche with higher levels of prenatal PFOA exposure were reported, but with no particular explanation. The effects of BFRs on pubertal development were evaluated in girls exposed *in utero* to polybrominated biphenyls (PBBs) and through breastfeeding. In this case girls exposed *in utero* to high concentrations of BFRs and breastfed had menarche one year earlier than girls not exposed or exposed only *in utero* but not breastfed. Perinatal exposure was associated with early puberty in breastfed girls (Lucaccioni et al., 2020; Street and Bernasconi, 2020). These results support the hypothesis that total pubertal development may be

influenced by pre- and postnatal exposure to organochlorine compounds. Also, since menarche and breast development are estrogen-dependent, while pubic hair development is independent of estrogen levels, these data suggest that PBBs may act through different pathways. Likewise, associations between prenatal and childhood exposure to PBDEs and changes in pubertal development were indicated (Lucaccioni et al., 2020; Street and Bernasconi, 2020). Concentrations of four PBDEs (BDE- 47, -99, -100, -153) were determined in serum taken from mothers during pregnancy, and the onset of puberty was assessed in their 9-year-old children, who were followed until age 13. According to this study prenatal concentrations of PBDEs were associated with delayed menarche in women.

3.4.2. Male reproductive system

Hypospadias and cryptorchidism were related to EDCs since the first studies led to the hypothesis of the testicular dysgenesis syndrome (Predieri et al., 2022). EDCs seem to act on the tubular part of the testicle, which does not develop regularly and is at subsequent risk of cancer, and the endocrine part with consequent lower production of testosterone and other endocrine factors necessary to ensure the normal testicular descent in the scrotum and the normal penile formation. Several examples of the effect of EDCs on such conditions are available in the literature. However, a full study on this topic is still lacking. The results of a research published by Fisher et al. (Fisher et al., 2021) indicate that maternal serum BPA levels at 10-17 weeks of gestation were positively associated with congenital or postnatal acquired cryptorchidism. Also prenatal exposure to dioxins and chlorinated pesticides can result in cryptorchidism (Gore et al., 2015). In addition, high rates of hypospadias have been reported in children whose mothers were exposed to phthalates and their metabolites during the first or second trimester of pregnancy (Jensen et al., 2015; Ormond et al., 2009). In the case of PFAS, maternal exposure was associated with decreased anogenital distance in boys, providing evidence that they may affect male genital development (Tian et al., 2019).

3.4.3. Female reproductive system

Compared to the effects of prenatal, perinatal and postnatal exposure to EDCs on the male reproductive system, the female reproductive system is not as widely described. Most of the available literature has

focused attention on delayed or early puberty, but there are few items describing possible diseases and physiological dysfunctions associated with early exposure to EDCs. This is due, among other things, to the great complexity of the functioning of the female reproductive system and the multitude of factors affecting its proper functioning. For example, it is well known that during pregnancy the human fetal adrenal glands (both male and female) are essential for the production of steroid hormones. However, it is the female hypothalamic-pituitary-adrenal axis that appears to be more susceptible to programming in early life than the male, and thus potentially to EDCs (Carpenter et al., 2017). Yet, it is still unclear how exactly this affects the programming of the reproductive system in women.

What is known is that a woman's reproductive health is largely determined during embryonic and fetal development, and later in adolescence (Van Duursen et al., 2020). Disorders of the female reproductive system in adulthood can be attributed to disturbances in hormone levels and function during *in utero* development, what was clearly demonstrated in the "DES disaster," where overt reproductive effects were described in children born to women taking the synthetic estrogen diethylstilbestrol (DES) as a drug during pregnancy (Patisaul, 2021). Adverse health effects included a rare form of vaginal cancer in girls, an increased incidence of uterine fibroids, endometriosis, impaired fertility and an earlier age of onset of menopause (Van Duursen et al., 2020). Surprisingly, reproductive effects are still seen in women whose mothers were prenatally exposed to DES (Titus et al., 2019).

At birth, there are about 300,000 primary follicles containing eggs or oocytes per ovary, which constitutes the ovarian reserve. A woman's ovarian reserve is finite, which means that lost oocytes cannot be replaced, which is a major factor limiting human reproduction. The possible actions of EDCs such as BPA and DEHP on the developing oocytes and ovary have been described in a review by Johansson et al. (Johansson et al., 2017). The likely influence of EDCs on the formation of ovarian abnormalities, defects in the resulting oocytes and an increased risk of cancer in the reproductive system have been pointed out. However, the female reproductive system is very different in the embryo, fetus, newborn, young girl, teenager and adult woman. Consequently, the final effects of EDCs exposure on the female reproductive system depend on the age of the woman and the exact life stage at which the exposure occurred.

4. Sources of exposure

Humans are continuously exposed to a cocktail of both natural and anthropogenic chemicals with endocrine-disrupting potential through diet, inhalation, or dermal absorption. Naturally occurring compounds such as metals, metalloids, and polycyclic aromatic hydrocarbons occur in the surrounding environment mainly as a result of metal mining and the combustion of fossil fuels. Whereas anthropogenic chemicals are commonly used in agricultural practices or are released from many different materials and products. Many EDC are currently used in a wide range of consumer goods, including personal care products, food containers and other plastic products, household items, cookware, pharmaceuticals, medical supplies, furniture, and building materials (Padmanabhan et al., 2021; Plante et al., 2022). Moreover, they are also used in the production of many products intended for infants and children (plastic bottles, teeters, toys, clothes, and food) (Kiess et al., 2021). Among the most frequently identified endocrine active compounds in such products can be distinguished: bisphenols (BPs), phthalates (PAEs), benzophenones (BPs), PCBs, polyfluorinated compounds (PFCs), parabens, and PBDEs. **Figure 2** shows different sources of EDC exposure for both adults and children. It should be borne in mind that exposure to EDC compounds begins at the stage of prenatal development and lasts until the end of life. Whereas, the uptake of EDCs varies according to age and depends on many factors, such as culture, socio-economic status, level of education, lifestyle factors, and food habits (Caspersen et al., 2016; Martina et al., 2012). Below, the different sources of exposure for both pregnant women and babies will be discussed.

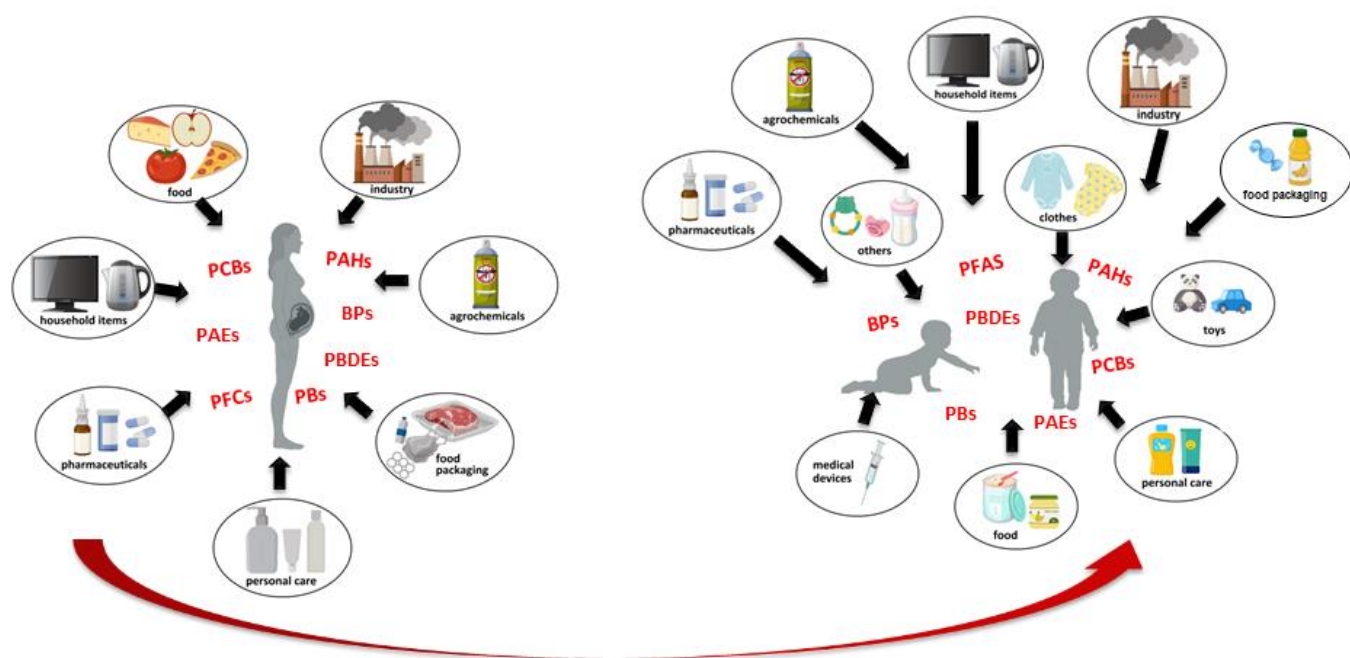


Figure 2. Schematic representation of different sources of exposure for both pregnant women and babies.

4.1. Prenatal exposure

The placenta is an important selective barrier to toxicants during pregnancy, however, nowadays it is known that some EDCs can be transferred to the fetus by interfering with placental transport systems. Several previous studies have reported that certain endocrine active compounds can pass the placental barrier (Song et al., 2020a). Thus, prenatal exposure of pregnant mothers to EDCs is directly correlated with fetal exposure to these chemicals. The mechanism of crossing the placental barrier of chemicals depends on many factors such as molecular size, protein binding capacity, or lipophilicity hence is not fully recognized so far. However, because EDCs are mostly lipophilic, passive diffusion appears to be the most likely mechanism (Kawa et al., 2021; A. Li et al., 2019; Zhang et al., 2022). Several mother-infant pair studies have reported the occurrence of EDCs in cord serum and amniotic fluid indicating transplacental transfer of xenobiotics from mother to fetus. In **Table 2**, there are summarized examples

809 of compounds detected in maternal samples as well as placenta, cord plasma, and amniotic fluid,
810 indicating transplacental transfer.

811

812 Based on the data presented in the table, it can be concluded that, generally the xenobiotic levels detected
813 in cord plasma is similar or lower than those reported for maternal plasma. Whereas in the case of
814 amniotic fluid, the detected level is higher in most cases. What could be particularly unfavourable due
815 to this fluid surrounds the unborn baby throughout the entire period of pregnancy (Shekhar et al., 2017).

Table 2. EDCs concentration levels in a placenta, cord plasma, amniotic fluid, breast milk, urine, and blood of pregnant women.

Class of EDC	Compound	Maternal urine	Maternal plasma	Maternal serum	Placenta	Cord plasma	Amniotic fluid
Bisphenols	BPA	T ₁ 13.04 [ng/mL]	5.83 [ng/mL]	T ₁ <MDL - 67.6	<LOD-43.2	1.7 [ng/mL]	5.87 [ng/mL]
		T ₂ 8.38 [ng/mL]	(Shekhar et al., 2017)	[ng/mL]	[μg/L]	(Zhang et al., 2020)	(Shekhar et al., 2017)
		(Huang et al., 2019)		T ₃ 0.71 - 11.6 [ng/mL]	(J. Lee et al., 2018)		
		T ₁ 0.06 [ng/mL]	0.023-0.084	0.5 [ng/mL]	26.0–908 [pg/g]	0.049-0.30 [ng/mL]	0.2 [ng/mL]
		T ₃ 0.07 [ng/mL]	[ng/mL]	(Zhang et al., 2020)	(Pan et al., 2020)	(Kolatorova et al., 2018)	(Zhang et al., 2020)
		(Foster et al., 2019)	(Kolatorova et al., 2018)				
		T ₁ 2.37±4.02 [μg/L]	113–416 [pg/g]	0.44-47.1 [μg/L]	1.30 [ng/g w.w.]	54.0–253 [pg/g]	
		T ₃ 2.70±5.79 [μg/L]	(Pan et al., 2020)	(J. Lee et al., 2018)	(Freire et al., 2020)	(Pan et al., 2020)	
		(Wang et al., 2021)					
		1.85 [ng/mL]					
		(Chen et al., 2022)					
		0.3–61.8 [μg/L]					
		(Casas et al., 2016)					

T₂ 35.22 [μg/L]

(Martínez-Ibarra et al., 2019)

BPS	T ₁ 4.43 [ng/mL]	<LOD–54.7 [pg/g]	0.01 [ng/mL]	<LOD–66.8	0.03 [ng/mL]	0.02 [ng/mL]
	T ₃ 4.60 [ng/mL]	(Pan et al., 2020)	(Zhang et al., 2020)	[pg/g]	(Zhang et al., 2020)	(Zhang et al., 2020)
	(Huang et al., 2019)			(Pan et al., 2020)		
	T ₁ 0.82±2.09 [μg/L]				<LOD–31.3 [pg/g]	
	T ₃ 0.73 ± 2.08 [μg/L]				(Pan et al., 2020)	
BPF	T ₁ 2.46±6.98 [μg/L]	<LOD–257 [pg/g]		<LOD–89.2		
	T ₃ 2.29±5.25 [μg/L]	(Pan et al., 2020)		[pg/g]		
	(Wang et al., 2021)			(Pan et al., 2020)		
Phthalates	MEP	21.9–5115.1 [μg/L]	3.11 [ng/mL] (Assens			20.88 ± 31.12 [μg/mL]
		(Casas et al., 2016)	et al., 2019)			(Golestanzadeh et al.,
	T ₁ 9.97 [ng/mL]		<LOD–21.07 [ng/mL]			2022)
	T ₃ 13.51 [ng/mL]		(Henriksen et al., 2020)			
		(Grindler et al., 2018)				
	T ₁ 11.12 [ng/mL]					

	T ₃ 10.32 [ng/mL]		
	(Han et al., 2020)		
	<hr/> T ₁ 37.6 ± 3.8 [μg/L]		
	T ₃ 42.1 ± 4.5 [μg/L]		
	(Shaffer et al., 2019)		
MnBP	3.4–402.6 [μg/L]	1.27 [ng/mL]	2.4–24.5 [μg/L]
	(Casas et al., 2016)	(Assens et al., 2019)	(Katsikantami et al., 2020)
	<hr/> T ₂ 101.3 [μg/L]	<hr/> <LOD-463 [ng/mL]	<hr/> 20.88 ± 31.12
	(Martínez-Ibarra et al., 2019)	(Henriksen et al., 2020)	(Golestanzadeh et al., 2022)
	<hr/> T ₁ 42.97 [ng/mL]		
	T ₃ 55.63 [ng/mL]		
	(Grindler et al., 2018)		
	<hr/> T ₁ 8.3 ± 2.4 [μg/L]		
	T ₃ 9.7 ± 2.7 [μg/L]		
	(Shaffer et al., 2019)		

MEHP	T ₂ 12837 [µg/L]	3.07 [ng/mL]	
	(Martínez-Ibarra et al., 2019)	(Assens et al., 2019)	
	T ₁ 2.5 ± 2.5 [µg/L]	<LOD-32.2 [ng/mL]	
	T ₃ 2.1 ± 2.4 [µg/L] (Shaffer et al., 2019)	(Henriksen et al., 2020)	
MCOP	T ₁ 19.3±3.5 [µg/L]	<LOD-7.58 [ng/mL]	
	T ₃ 16.0±3.3 [µg/L] (Shaffer et al., 2019)	(Henriksen et al., 2020)	
MBzP	T ₂ 1.86 [µg/L]	<LOD-73.8 [ng/mL]	8.89 ± 7.22 [µg/mL]
	(Martínez-Ibarra et al., 2019)	(Henriksen et al., 2020)	(Golestanzadeh et al., 2022)
			11.6-20.2 [µg/L]
			(Katsikantami et al., 2020)
ΣDEHP	T ₁ 198.2 [ng/mL]	7.44 [ng/mL] (Assens	
	T ₃ 159.3 [ng/mL]	et al., 2019)	
	(Grindler et al., 2018)	<LOD-16.0 [ng/mL]	
		(Henriksen et al., 2020)	

Parabens	MeP	T ₁ 1.4-4770.7 [µg/L] (Bellavia et al., 2019)	8.04 [ng/mL] (Shekhar et al., 2017)	<0.01-10 [ng/mL] (Song et al., 2020b)	1.45 [ng/g w.w.] (Freire et al., 2020)	0.066-4.14 [ng/mL] (Kolatorova et al., 2018)	8.69 [ng/mL] (Shekhar et al., 2017)
		T ₁ 18.06 [µg/L]	0.18-1.62 [ng/mL]		0.10-11.69	<0.01-9.5 [ng/mL]	<0.01-2.7 [ng/mL]
		T ₃ 12.16 [µg/L] (Liu et al., 2019)	(Kolatorova et al., 2018)		(Fernández et al., 2016)	(Song et al., 2020b)	(Song et al., 2020b)
		T ₁ 20.76 [µg/L]					
		T ₃ 11.24 [µg/L] (Jiang et al., 2019)					
		132.43 [ng/mL] (Chen et al., 2022)					
		T ₁ 15.37 [ng/mL]					
		T ₃ 9.82 [ng/mL] (J. Li et al., 2019)					
	EtP	T ₁ 0.66 [µg/L]	2.27 [ng/mL]	<0.01-6.5 [ng/mL]	0.29 [ng/g w.w.]	<0.01-6.4 [ng/mL]	2.30 [ng/mL]
		T ₃ 0.4 [µg/L] (Liu et al., 2019)	(Shekhar et al., 2017)	(Song et al., 2020b)	(Freire et al., 2020)	(Song et al., 2020b)	(Shekhar et al., 2017)
		T ₁ 0.55 [µg/L]					<0.01-0.26 [ng/mL]
		T ₃ 0.39 [µg/L]					(Song et al., 2020b)

	(Jiang et al., 2019)			0.20-5.49		
	T ₁ 0.51 [ng/mL]			(Fernández et al.,		
	T ₃ 0.53 [ng/mL] (J.			2016)		
	Li et al., 2019)					
PrP	T ₁ <LOD –621	9.14 [ng/mL]	<0.01-1.8 [ng/mL]	0.27 [ng/g w.w.]	0.046-0.78 [ng/mL]	10.76 [ng/mL]
	[µg/L]	(Shekhar et al.,	(Song et al., 2020b)	(Freire et al.,	(Kolatorova et al.,	(Shekhar et al., 2017)
	T ₂ <LOD –2291	2017)		2020)	2018)	
	[µg/L]					
	(Bellavia et al., 2019)					
	T ₁ 1.10 [µg/L]	0.031-0.24 [ng/mL]		0.20-4.52	<0.01-2.6 [ng/mL]	<0.01-1.1 [ng/mL]
	T ₃ 0.61 [µg/L]	(Kolatorova et al.,		(Fernández et al.,	(Song et al., 2020b)	(Song et al., 2020b)
	(Liu et al., 2019)	2018)		2016)		
	T ₁ 1.02 [µg/L]					
	T ₃ 0.4 [µg/L]					
	(Jiang et al., 2019)					
	26.78 [ng/mL]					
	(Chen et al., 2022)					
BuP	0.61 [ng/mL]		<0.01-0.47 [ng/mL]		<0.01-0.52 [ng/mL]	2.37 [ng/mL]
	(Chen et al., 2022)		(Song et al., 2020b)		(Song et al., 2020b)	(Shekhar et al., 2017)

		1.96 [ng/mL] (Shekhar et al., 2017)	0.20-1.60 (Fernández et al., 2016)	<0.01-0.033 [ng/mL] (Song et al., 2020b)
Phenols	BP-1	T ₁ 0.34 [µg/L]	<LOD – 4.37 [ng/mL]	<0.02–52.0 [ng/mL]
		T ₂ 0.24 [µg/L]	(Krause et al., 2018)	(Song et al., 2020a)
		T ₃ 0.20 [µg/L] (Jiang et al., 2019)		(Krause et al., 2018)
		<LOD – 665 [ng/mL] (Krause et al., 2018)		
		T ₁ 0.31 [ng/mL]		
		T ₃ 0.19[ng/mL] (J. Li et al., 2019)		
	BP-3	T ₁ 0.75 [µg/L]	<LOD – 71.8 [ng/mL]	<0.01–56.6 [ng/mL]
		T ₃ 0.38 [µg/L] (Jiang et al., 2019)	(Krause et al., 2018)	(Song et al., 2020a)
		<LOD – 10034 [ng/mL] (Krause et al., 2018)		(Krause et al., 2018)
		T ₁ 0.52 [ng/mL]		

T₃ 0.29 [ng/mL]
(J. Li et al., 2019)

Pesticides	NP	7.61 [ng/mL] (Shekhar et al., 2017)	7.79 [ng/mL] (Shekhar et al., 2017)
	OP	3.69 [ng/mL] (Shekhar et al., 2017)	3.10 [ng/mL] (Shekhar et al., 2017)
	TCS	3.1 ± 4.2 [ng/mL] (Bai et al., 2020)	7.15 [ng/mL] (Shekhar et al., 2017)
		3.3 ± 9.8 [ng/mL] (Bai et al., 2020)	2.5 ± 5.3 [ng/mL] (Bai et al., 2020)
		T ₁ 0.48 [ng/mL] T ₃ 0.32 [ng/mL] (J. Li et al., 2019)	7.81 [ng/mL] (Shekhar et al., 2017) 0.56 ± 0.14 [ng/mL] (Bai et al., 2020)
	HCB	6.3–114 [ng/g] (Caspersen et al., 2016)	T ₁ 103.8 [pg/mL] (Vafeiadi et al., 2017) <LOD-0.715 [ng/mL] (Barmpas et al., 2020)

Perfluoroalkyl substances	p,p'-DDE	13.8–1375 [ng/g] (Caspersen et al., 2016)	T ₁ 2067.9 [pg/mL] (Vafeiadi et al., 2017)	263.3 ± 50.7 [μg/kg] (Toichuev et al., 2018)	0.65-8.81 [ng/mL] (Luo et al., 2017)	0.001-2.796 [ng/mL] (Barmpas et al., 2020)
	PCB153	<LOD-116 [ng/mL] (Müller et al., 2019)	T ₁ 141.6 [pg/mL] (Vafeiadi et al., 2017)			
		12.8–133 (Caspersen et al., 2016)				
	PCB180	6.9–142 [ng/g] (Caspersen et al., 2016)	T ₁ 73.8 [pg/mL] (Vafeiadi et al., 2017)			
	PFHxS	T ₁ 1 [μg/L] (Fisher et al., 2016)	<LOD-0.73 [ng/mL] (Fisher et al., 2016)		0.05-0.83 [ng/mL] (Gao et al., 2019)	
			<LOD-1.15 [ng/mL] (Gao et al., 2019)			
	PFOA	T ₁ 1.7 [μg/L] (Fisher et al., 2016)	<LOD-1.13 [ng/mL] (Müller et al., 2019)		0.39 [μg/L] (Fisher et al., 2016)	

		0.6–8.0 [ng/g] (Mamsen et al., 2017)	<LOD-25.4 [ng/mL] (Gao et al., 2019)	0.04–0.45 [ng/g] (Mamsen et al., 2017)	0.03-10.2 [ng/mL] (Gao et al., 2019)
	PFOS	T ₁ 4.6 [µg/L] (Fisher et al., 2016)	<LOD-1.54 [ng/mL] (Müller et al., 2019)	0.3–3.1 [ng/g] (Mamsen et al., 2017)	0.04-8.01 [ng/mL] (Gao et al., 2019)
		2.5–16.7 [ng/g] (Mamsen et al., 2017)	0.07-22.6 [ng/mL] (Gao et al., 2019)		
	PFAS and PFAS		0.01-6.71 [ng/mL] (Cai et al., 2020)		0.04.-2.66 [ng/mL] (Cai et al., 2020)
	PBDE-28	0.04–0.5 [ng/g] (Caspersen et al., 2016)	0.015 [ng/g] (Zota et al., 2018)	0.2 [ng/g] (Matovu et al., 2020)	0.1 [ng/g] (Matovu et al., 2020)
Polybrominated substances	PBDE-47	<LOD–9.1 [ng/g] (Caspersen et al., 2016)	0.17 [ng/g] (Zota et al., 2018)	0.25 [ng/g] (Matovu et al., 2020)	0.03 [ng/g] (Matovu et al., 2020)

BPS-Bisphenol S; BPF-Bisphenol F; MeP – methylparaben; PrP-Propylparaben; MnBP - Mono-n-butyl phthalate; MEHP - Mono-(2-ethylhexyl) phthalate; MCOP- Mono-carboxy-isooctyl phthalate; MBzP- monobenzylphthalate; DEHP- Di(2-ethylhexyl)phthalate; MeP- methylparaben; EtP- Ethylparaben; PrP-Propylparaben; BuP- Butylparaben; BP-1- benzophenone-1; BP-3- benzophenone-3; NP-nonylphenol; OP-octylphenol; TCS-triclosan; HCB-hexachlorobenzene; p,p'-DDE- dichlorodiphenyldichloroethylen; PCB153- ,2,2',4',5,5'-Hexachlorobiphenyl; PCB

180-2,2',3,4,4',5,5'-heptachlorobiphenyl; PFHxS- perfluorohexanesulfonate; PFOA- perfluorooctanoic acid; PFOS- Perfluorooctanesulphonate; PBDE-28- 2,4,4'-tribromodiphenyl ether; PBDE-47- 2,2',4,4'-tetrabromodiphenyl ether; T₁, T₂, T₃- 1st, 2nd, 3rd trimesters

4.1.1. *Mummy's style of life*

As previously stated, fetal exposure is directly related to pregnant women's exposure to EDCs due to the maternal-fetal placenta transfer of contaminants. Thus, the lifestyle of the mother before and during pregnancy strictly determines the dose of pollutants to which the fetus will be exposed. Exposure via food and beverages is considered to be the major source. In the literature, one can find information that diet accounts for up to 90% of exposure to BPs, PCBs, PAEs, and OCPs (organochlorine pesticides) (Kiess et al., 2021; Padmanabhan et al., 2021). These contaminants may be present in food as contaminants from the environment, food contact materials, and food processing utensils and equipment (Padmanabhan et al., 2021). Therefore, both the food preferences and habits i.e. type and the quantity of food consumed by pregnant women can influence their dietary intake of EDCs. Bisphenols and phthalates were most often found in different kinds of products such as: milk-based products (Herrero et al., 2021), soft drinks, juices (Kumar et al., 2022; Tzatzarakis et al., 2017), canned vegetables, fruits, and meats (Lorber et al., 2015; Szczepańska et al., 2020). The high concentrations of BPA and its analogues are also noted in seafood and fish (Gardener et al., 2022). Several studies have found significant correlations between urinary and blood BPA concentrations and consumption of canned food and food stored in plastic containers (Hartle et al., 2016; Peng et al., 2019; Snoj Tratnik et al., 2019). Moreover, consumption of food re-heated in plastic containers was also associated with a higher urinary BPA level (Haq et al., 2020; Snoj Tratnik et al., 2019). What is more, in several studies, the dependence between increased BPA (Ami R. Zota, Cassandra A. Phillips, 2016) and phthalates (Smith et al., 2022; Varshavsky et al., 2018) exposure was also connected with increased consumption of fast foods and ultra-processed foods (Buckley et al., 2019). One study reported, 20% higher BPA urinary level of pregnant women who reported eating hamburgers three times per week or more compared to women who reported not consuming any hamburgers (Quirós-Alcalá et al., 2013). Numerous epidemiological studies have shown that consuming high-fat foods, such as fish, dairy products, red meat, and eggs, is a main source of exposure to PCBs and OCPs (Harmouche-Karaki et al., 2019; Witczak and Abdel-Gawad, 2014). A few findings also demonstrated the role of fruits and vegetable consumption in influencing serum levels of PCBs and OCPs (Arrebola et al., 2018; Helou et al., 2021; H. A. Lee et al., 2018). Similarly, the eating of grilled or charred foods such as meats is indicated as the main source of

exposure to PAHs, which are other known EDCs (Alomirah et al., 2011). It should be noted that throughout pregnancy, the mother's body goes through physiologic changes, increasing the need for energy and the amount of food and water consumed (Plante et al., 2022). As a result, during pregnancy, exposure to EDCs may increase. Another important source of women's exposure to EDCs is the use of personal care products. The main endocrine active compounds occurred in cosmetics are parabens, benzophenone-UV filters and phthalates. Over the past years, these synthetic compounds have been commonly found in body lotions, skin care products, shampoos, deodorants, and lipsticks. These compounds applied to the skin along with the cosmetic are easily absorbed and thus enter the body (Martín-Pozo et al., 2021). The use of personal care products corresponded positively to the detection of phthalate metabolites and paraben metabolites (Martín-Pozo et al., 2021; Pagoni et al., 2022) in urine samples. Some EDC can also be emitted into the indoor environment. Some reports showed that PAEs, PBDEs, PFAAs, PCBs, and PAHs can be released from vinyl floor (Benning et al., 2013), carpets (Lucattini et al., 2018; Vojta et al., 2017), upholstery (Harris et al., 2021; Lucattini et al., 2018), nonstick cookware (Sajid and Ilyas, 2017), electronics devices (Yang et al., 2020), paints and other widely used materials in buildings (Hou et al., 2018; Teil et al., 2016).

4.2. *Infant and early-life children exposure*

Early life exposure to EDCs and related chemicals have been associated with many diseases. As per some reports, 99–100% of pregnant women tested positive for the presence of several chemical classes, including PCBs, organochlorine pesticides, PFASs, PBDEs, phthalates, and PAHs (Woodruff et al., 2011). Given that numerous of these substances have been found in amniotic fluid and cord blood, it is obvious that the placenta does not shield the fetus from exposure (De Cock et al., 2017). Newborn TSH levels are impacted by early exposure to PCB-153 and p,p'-DDE. Higher exposure levels were linked to TSH levels that were 12–15% lower (De Cock et al., 2017).

4.2.1. *Medical devices*

Medical supplies are substantial source of exposure to numerous types of EDCs, such as phthalates, bisphenol A, parabens, perfluoroalkyl compounds, and triclosan. Some of the EDCs were detected in syringes, microcapillary blood tubes and venous catheters. Evidence of release into parenterally given solutions, including many parabens, phthalates, and other suspected EDCs, may be of much greater concern. The release of phthalates from medical use polymers is not surprising as they make 30-40% of such polymers and generally non-covalently bonded. Although the countries like France restricted the use of phthalates in medical goods, still the hospital exposure occurred through extracorporeal membrane oxygenators, blood transfusion sets, and intravenous extension lines. Because of their all-encompassing antibacterial action, parabens are frequently employed in medical products. For methylparaben, their concentrations in intravenous solutions might reach 0.72%. Additionally, parabens are used in ultrasonic gels because of their bacteriostatic properties. To avoid bloodstream infections brought on by catheters, several hospitals additionally include parabens into their heparin lock solutions. The release of BPA has also been linked to medical supplies (Genco et al., 2020).

The population of Neonatal Extensive Care Units (NICU) is at significant risk as a result of the frequent and intensive medical interventions, neonates' reduced capacity to eliminate toxic pollutants, and their increased vulnerability to endocrine disruptors. Recently, a study was conducted to measure the exposure of NICU patients to PVC medical device plasticizers and it was compared with those discharged from the hospital. DEHP and TEHTM metabolites urinary concentrations were lower at discharge compared to NICU. The primary sources of exposure were medical devices used for respiratory support, infusion treatment, enteral nutrition, and transfusion. The babies' exposure was considerably elevated by smaller gestational age and body weight (Bernard et al., 2023).

Similarly, research was designed to find the exposure of BPA through nutritional intake and medical devices. Mother and the premature infants who were in NICU for last 3 days were registered for this study. One sample of nutritional intake (breast milk or formula) was collected from 43 mothers and two samples of urine (before and after nutritional intake) were collected from the infants. The median urinary total BPA concentration among infants who needed the use of 4 or more medical devices in the past 3 days was significantly higher (36.6 µg/L) than among infants who required 0 to 3 devices (13.9 µg/L).

Exposure to BPA was positively correlated with the quantity of medical equipment used during the previous three days but not with dietary consumption (Duty et al., 2013).

4.2.2. Food

Food contaminated with chemicals poses a serious risk to human health and is a major global food safety problem. Both manmade and naturally existing environmental variables can contaminate food. Food items have been shown to include several chemical groups concurrently, including those from metal(oids), polycyclic aromatic hydrocarbons, persistent organic pollutants, perfluorinated compounds, radioactivity, plastics, and nanoparticles. Additionally, when consumed in significant doses, several ingredients used in food processing, such as emulsifiers and artificial sweeteners, may be damaging to consumers' health. Eating contaminated food is the main exposure pathway for the majority of human and animal populations (Calatayud Arroyo et al., 2021).

Phytoestrogens, phthalates, POPs, pesticides, bisphenol A and many other EDCs are found in the food items. The contaminated foods may include eggs, breast milk and drinking water. The infants can be exposed to EDCs through the breast milk as well as infant formula, as the presence of such chemicals have been reported in both of them. The mammary gland of nursing mothers is concentrated with highly lipid-soluble compounds. So, breast milk with a high lipid content in particular carries a greater risk. Additionally, the number of births, length of breastfeeding, and mother age all have an impact on the level of exposure. The contaminated drinking water can be another source (Ercan and Tarcin, 2022).

Depending on physicochemical conditions like temperature, UV light, pH, microwave, and mechanical stress, EDCs can migrate as residual monomers, additives used in polymeric material of food containers (Bang et al., 2012). Phthalates can be the common EDCs coming from the food packaging (Meeker, 2012).

OCPs and some metals were found in infant formula and baby foods in Turkey (Kilic et al., 2018). 4-Nonylphenols (NPs) were analyzed in 60 commercial foods in Germany. Regardless of the food's fat content, the concentrations of NPs on a fresh weight basis ranged between 0.1 and 19.4 µg/kg (Guenther et al., 2002). A study was designed to study the presence of bisphenol analogues (BPA, BPAF, BPC,

BPE, BPFL, BPS, and BPZ) in powdered baby formula from several Indian brands and to calculate the dietary exposure to these substances for infants aged 0 to 12 months. BPA (mean = 5.46 ng/g) had the highest concentration, followed by BPZ and BPS. There was no evidence of BPAF, BPFL, BPC, or BPE detection in any of the samples (Karsauliya et al., 2021). In another study, infants who were solely breastfed had lower total BPA metabolite concentrations than those who were exclusively formula-fed or breastfed with supplements (Fisher et al., 2019). There are many reports on migration of BPA from canned bottles to the foods (A. Goodson, 2002; Biles et al., 1997).

4.2.3. *Personal care products and cosmetics*

Cosmetics and personal care products (PCPs) are essential items in our everyday lives. Since they are so widely used, some toxins that people ordinarily wouldn't be exposed to might potentially be exposed through them. UV filters, parabens, phthalates, synthetic musks, and other antimicrobial compounds are commonly used in cosmetics and PCPs. Like benzophenones in sunscreens or parabens used as preservatives and antimicrobials, the majority of EDCs are purposefully included in PCP formulations. Additionally, several of these substances have the potential to passively migrate into the PCP over time if they are not chemically bonded to the polymer matrix. When the component can be extracted under severe circumstances, typically by laboratory manipulation, they are referred to be leachable and extractable in this context (Martín-Pozo et al., 2021).

One study investigated the relationship between phthalate metabolite concentrations in infant urine and maternal reported use of infant skin care products. This study measured the concentrations of 9 phthalate metabolites in 163 infants born in 2000-2005. In 81% of the infants, the concentrations of 7 phthalate metabolites were above the LOD. Increased urinary concentrations of monoethyl phthalate, monomethyl phthalate, and monoisobutyl phthalate were found in infants exposed to lotion, powder, and shampoo, and these connections become stronger the more items were used. Young newborns may be particularly susceptible to the developmental and reproductive toxicity of phthalates due to their underdeveloped metabolic systems and greater dose per unit body surface area. This link was highest in this population (Sathyanarayana et al., 2008). In another study investigated 11 PAEs in 198 PCPs collected from the

market of Shanghai and it was found DEP was the most detected compounds (29.8%) and other PAEs were also detected (Bao et al., 2015). The phthalate metabolite concentrations in infant urine were higher when baby lotion or baby powder had been applied to them within the preceding 24 hours (Fisher et al., 2019).

4.2.4. Toys

Due to physiological differences (e.g., lower metabolic capacity compared to adults) and unique exposure patterns, such as hand-to-mouth behavior, young children, especially those under the age of 36 months, are thought to be more sensitive to chemical substance exposure. Additionally, windows of vulnerability to substances with endocrine action are associated with developmental phases. This may account for the rising prevalence of some conditions, including those that affect the reproductive system or neurodevelopmental problems. Children put a wide variety of things in their mouths, including toys, according to several studies based on observations of children's mouthing behavior between the ages of 0 and 36 months. To produce plastic toys, complicated combinations of one or more polymers are frequently used, along with several additives including plasticizers, flame retardants, and antioxidants. Plastics have been demonstrated to leak compounds like phthalates or UV filters, which are recognized endocrine disruptors, since some of these ingredients are not covalently bonded to the polymers (Kirchnawy et al., 2020). A Directive that governs toys in the European Union forbids the use of carcinogenic, mutagenic, and reprotoxic (CMR) compounds in categories 1A, 1B, or 2 in toys or structurally independent pieces, unless the ingredient is inaccessible or present in amounts below a certain level. In a recent study, migration experiments of toys were conducted in saliva simulants. Nine out of the 18 toys that were evaluated had discernible estrogenic action. By identifying the well-known endocrine active chemical BPA in two samples, the discovered estrogenic activity could be well explained. Analysis of 41 known or suspected endocrine active substances in plastic failed to explain the origin of the estrogen activity in seven out of nine estrogen-active samples, indicating that the estrogen activities were caused by endocrine active substances that are currently unknown or that are not currently suspected in toys (Kirchnawy et al., 2020).

This is also fact that infants and toddlers are constantly exposed to toys at childcare. A study evaluated leaching of BPA and phthalates from the toys used at several day care facilities in Philadelphia and found an average leaching of 13–280 ng/cm² of BPA and phthalates (Andaluri et al., 2018). In another study, DEHP was the highest detected phthalate in toy sample (Praveena et al., 2021).

4.2.5. Clothes

Industrial textile production uses about 1900 chemicals, many of which (around 165) are deemed potentially harmful to humans and/or the environment. These chemicals include pesticides, plasticizers, dyes, antioxidants, and flame retardants, and others to achieve various effects in the cloths (Freire et al., 2019; K. Lacasse, 2012; Swedish Chemicals Agency, 2013). Human exposure to environmental toxins is greatly influenced by clothing. On the one hand, limiting exposure to environmental toxins can protect humans. On the other side, clothes can also be a source of chemical exposure. Wearers of the cloths, especially children, can be exposed to these chemicals either directly or indirectly. Some of these chemicals may stay in the finished textile product, either purposefully or accidentally. Previous research has demonstrated that semi-volatile organic compounds (SVOCs) partition between clothes and air (Li and Kannan, 2018).

To give materials fire and heat resistance as well as wrinkle-free qualities, melamine-based resins are widely utilized in textiles. However, nothing is understood about the presence of melamine and its compounds in textiles. The levels of melamine, ammeline, ammelide, and cyanuric acid in 77 textile samples and infant clothes bought in Albany, New York, USA, were examined. All textile samples contained one or more target analytes. Melamine accounted for 52% of the total concentrations of the four analytes, making it the most prevalent component (Zhu and Kannan, 2020).

BPA and parabens were found in infants and children's socks in Spain. BPA was detected in 91% of socks at concentrations ranging from <0.70 to 3736 ng/g. Ethyl-paraben was detected in 100% of socks, followed by methyl- and propyl-paraben. 41% of socks extracts were estrogenic and 19% were anti-androgenic (Freire et al., 2019). Socks were shown to be the main source of cutaneous exposure to benzotriazoles and benzothiazoles in a study that examined multiple newborn apparel items (Liu et al.,

2017). One study found up to a few percent total amounts of 23 EDCs in pantyhose gathered from six different nations (Li and Kannan, 2018). Infant exposure to phthalates from cotton clothes was shown to be a major route for dermal absorption (H. L. Li et al., 2019). Printed graphics over the cloths are also thought to be the contributor of exposure to several chemicals (Liu et al., 2017).

4.2.6. Others

Water and milk bottles can also contribute to exposure of infants and early-life children to EDCs. BPA can release from the baby bottles under the normal use conditions (Li et al., 2010). Even at low dosages, infants are unquestionably the group most at risk from BPA exposure. BPA may have an impact on how the brain, prostate glands, and behavior of fetuses, neonates, and early children develop. The primary sources of BPA exposure for infants are the migration of BPA from the can liner into infant formula and from polycarbonate baby bottles. As a result, Canada and Europe have banned the use of BPA in baby bottles. The Tolerable Daily Intake (TDI) of BPA has been set by the European Food Safety Authority (EFSA) at 4 µg/kg body weight/day due to the risk that BPA presents to human health. The European standards defined the specific migration limits (SML) of BPA from plastics in contact with food at 600 µg/kg in 2011. New legislation decreased the SML threshold to a more restrictive amount of 50 µg/kg. However, BPA migration from varnishes or coatings applied to materials and goods especially intended for newborns and young children (under 3 years old) is not allowed (Karsauliya et al., 2021).

One research found that serum BPA levels of bottle-fed infants (n=30) were significantly higher than those of breast-fed infants (n=30) and it was concluded that bottle feeding seems to enhance the risk of BPA exposure to infants (Rhie et al., 2014). The migration of BPAAs was examined in baby bottles (20 brands) and sippy cups (13 brands) in Canada. BPS, BPA, BPF, BPAF, BPM, and BPTMC had detection frequencies (DF) of more than 50%, making them the most frequently found analytes in baby bottles. The only substances often detected in sippy cups were BPA, BPS, and BPF. The average BPA content in infant bottle leachate was 31.5 ng/L in the water simulant but was 1.4 times higher in

the 50% EtOH simulant (Siddique et al., 2021). Plastic water containers can also release BPA and phthalates to water (Notardonato et al., 2019).

5. Biological samples coming from infant and children of early stage life – a need for public awareness, analysis and biomonitoring

It is extremely important to conduct biomonitoring of infants and children of early stage life and to develop sensitive and reliable analytical procedures. The methods should make it possible to estimate the exposure to EDCs and to assess the short- and long-term impact of these exposures on human health (Becker et al., 2009; Eskenazi et al., 2007; Hoffman et al., 2018). In the case of the biomonitoring of some chemical compounds (e.g. phthalates), special care should be taken with regard to the sampling materials used in order to reduce the potential contamination of the sample (Arbuckle, 2010). Generally, determination of EDCs in biological samples is performed using accurate and sensitive analytical instruments. The most common methods for this purpose are high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) or gas chromatography coupled with tandem mass spectrometry (GC-MS/MS) (**Table 3**).

5.1. Breast milk monitoring

Mother's milk is the first and basic food of newborns, which provides not only the necessary nutrients (lipids, proteins, vitamins, minerals and saccharides) but also antibodies. Thanks to this, breastfeeding strengthens the immune system and protects the baby from the first infections and diseases. The World Health Organization (WHO) and others recommend exclusive breastfeeding for infants up to 6 months, followed by partial breastfeeding for at least 2 years. Unfortunately, although breastfeeding is very beneficial, breast milk, in addition to essential and valuable ingredients, also contains harmful xenobiotics, including EDCs. Therefore, breast milk appears to be a critical body fluid for biomonitoring, as it simultaneously provides information on the exposure of both the mother and the breast-fed infant (Bernasconi et al., 2022; Macheka-Tendenguwo et al., 2018).

Naturally, EDCs are present in breast milk in trace amounts and the milk itself is a very complex matrix, hence the use of sensitive and selective analytical methods in human milk biomonitoring is required. However, in addition to the need to use sensitive analytical methods, great care must also be taken in selecting the appropriate sample preparation technique. The sample pre-treatment step is critical when biomonitoring EDCs in complex matrices such as breast milk due to the presence of lipids and proteins that make the determination of target compounds difficult. Moreover, the analytes themselves do not make the task easier, because the ubiquity of EDCs (mainly bisphenols, phthalates and parabens) increases the risk of sample contamination during sampling, pre-treatment and analysis of these compounds. For example, it has been proven that the use of containers and breast pumps during sampling breast milk and the use of laboratory equipment with plastic parts can be a source of BPA contamination (Dualde et al., 2019). One of the popular sample preparation techniques for EDCs biomonitoring in breast milk is the QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method based on liquid-liquid partitioning with acetonitrile, followed by salting out of the aqueous layer and then a purification step by dispersive solid-phase extraction (Czarczyńska-Goślińska et al., 2021; Dualde et al., 2019; Tuzimski et al., 2020). For example, Czarczyńska-Goślińska et al. (Czarczyńska-Goślińska et al., 2021) used the QuEChERS method in the biomonitoring of bisphenols and parabens in human milk to assess the nutritional risk of breast-fed infants. The highest average concentrations of parabens in the tested samples were found for methylparaben (MeP), which is not surprising because MeP is the most commonly used paraben in cosmetics. Interestingly, the milk samples taken from the woman who declared avoiding the use of cosmetics during pregnancy and breastfeeding contained the lowest concentration of parabens. In the case of bisphenols, the highest average concentration was found for BPA, which was close to the average MeP concentration. However, the authors emphasize that the estrogenic activity of MeP is as much as 2.5-3 million times lower than that of estradiol, while the estrogenic activity of BPA is only 1-10 thousand times lower than that of estradiol. Therefore, the detection of BPA in breast milk, which may have a more significant effect on infants, is of much greater concern. This has been proven by determining the hazard quotient (the ratio of the potential exposure to a substance and the level at which no adverse effects are expected), which for BPA (0.0723-0.1266) are much higher than for MP (0.00063-0.00182). Nevertheless, the authors reassure that the margin of safety



is still high because the hazard index (sum of hazard quotient for BPA and parabens) is much lower than one.

Witczak et al. (Witczak et al., 2021) examined the concentration of selected OCPs in breast milk during lactation. OCPs were detected in most samples in the range of 0 to 7.5 ng/g lipids. It was shown that the concentration of OCPs decreased throughout the duration of lactation. Redundancy analysis showed that the diet of pregnant women has a significant impact on the concentration of pesticides in their milk. Therefore, the authors emphasize that avoiding excessive consumption of meat, fish, eggs and dairy products can reduce the content of OCPs in breast milk. However, the determined hazard quotients for OCPs were very low.

In conclusion, despite many reports in the literature regarding contaminants in breast milk, breastfeeding is still recommended and fully supported. Nevertheless, some studies indicate negative consequences in infants fed breast milk containing EDCs, such as reduced weight and/or length gain associated with exposure to BPA or PFAS (Braun, 2017; Vela-Soria et al., 2020). Therefore, there is a need for further monitoring of EDCs in human milk and risk assessment of infants.

5.1. Blood monitoring

The problems of the biomonitoring of infants and toddlers appear at the first stage of the research, i.e., taking a sample from a small patient. Sampling urine or saliva is a non-invasive procedure, while taking a child's blood samples multiple times is associated with both physical and mental discomfort for the patient and his parents. Hence, such research are most often based on samples of the mother's milk and blood taken from infants at one time in order to characterize postnatal exposure to a target chemical compounds (Walkowiak et al., 2001). Obviously, infant toxicokinetic is a complex issue, and studies based on a one-time measurement provide only a partial view of the infant's exposure profile. To overcome these limitations and simultaneously follow ethic, many scientists believe that modelling the concentration of chemicals in a patient's blood after birth is the most correct approach to creating an infant exposure profile. In the literature, we can distinguish the lactation exposure model (LEM) (Pan et al., 2009) and a physiologically based pharmacokinetic model (PBPK) (Verner et al., 2009). The LEM

model is a single measurement of the analytes concentration and multiplies it by the duration of the breastfeeding. This approach is based on a large simplification assuming either constant postpartum exposure or an exposure that increases with lactation and then remains constant after the end of the breastfeeding (Pan et al., 2009). In contrast, the PBPK model, to put it simply, is a mathematical representation of the physiological processes that govern the absorption, distribution, metabolism, and excretion of chemicals in the body. On the one hand, the PBPK model gives slight measurement errors, but on the other hand, it is complicated and can only be described with a computer code. Therefore, PBPK model is difficult to use, and it is more demanding to assess the influence of each factor included in the model. Taking the above into account, Stigum et al., (2015) proposed a two-compartment (mother and child lipid) pharmacokinetic model described by three easy equations, offering researchers a model that is simpler to apply and understand than PBPK model. The model equations use a number of the parameters, including measured concentration of analytes in mother's milk, baby and mother weight at birth and in subsequent months of life, extrapolated fat weight of baby and mother, duration of the breastfeeding, and the approximate amount of the mother's milk consumed. Stigum et al., (2015) used the proposed model to investigate the effect of hexachlorobenzene on the growth of infants in the first two years of life. Studies have shown that the concentration of HCB in babies after birth was low (median of 11.2 ng/g lipids). However, during the lactation period, the median concentration increased and reached a maximum (36.5 ng/g lipids) after 15 months. Following the end of the breastfeeding period, the median gradually decreased. Children exposed to HCB through breast milk reached levels 1-5 times higher than their mothers. The obtained results proved that the two-compartment pharmacokinetic model is more accurate than the LEM model and, simultaneously easier to implement than the PBPK model. Lenters et al., (2019) also used this model to determine the concentrations of PBDEs, PFAS, PCBs and OCPs in the blood of infants from birth to 24 months of age. The studies showed a positive relationship between the concentration of β -HCH (median 4.37 ng/L in breast milk, median 4.14-12.02 ng/g in toddlers under 2 years of age) and PFOS (median 117 ng/L in breast milk) in breast milk and ADHD, with a suggestion that PFOS only affects the female sex (**Table 3**).

By contrast, Verner et al., (2010) used the PBPK model to simulate the levels of PCBs in the blood during the prenatal and postnatal periods and to assess the relationship of these levels to infant



behaviour. The authors showed that exposure to PCBs in early stage life induced behavioural changes in attention and activity levels. The median concentration of PCBs in the blood was 103 ng/g lipids, and the maximum analytes concentration was reached immediately after birth for bottle-fed infants and at the end of the lactation period for breast-fed infants (**Table 3**). However, the authors emphasize that the risks to the baby, even with relatively high levels of PCBs exposure, are unlikely to outweigh the benefits of breastfeeding.

5.2. Urine biomonitoring

As already mentioned, biomonitoring of the babies by sampling their urine is more acceptable for parents and children, less invasive and relatively easy to perform compared to the blood matrix. In the case of toddlers who have a diaper, it is possible to use paediatric urine bags for sampling (Fluegge et al., 2016). Unfortunately, the younger the child, the more difficult it is to conduct biomonitoring studies using urine samples. From birth to 12 months of age, the volume of urine available for sampling from toddlers per evacuation is usually less than 10 ml per sample and is slightly higher in children from 2 to 3 years of age. As children reach the age of 4-11 years, urine sampling becomes somewhat easier as the urine volume is approximately from 30 to 50 ml per evacuation (Barr et al., 2005). Although toddlers urinate more often, older children can control the timing of urination, which is quite an important convenience in the biomonitoring process. Another problem is that urine is an unregulated body fluid which composition and volume can vary between evacuations. In order to overcome this difficulty, the most common practice is a creatinine adjustment of the urinary metabolites to calculate the urine dilution (Bradman and Whyatt, 2005). Collection of all urine samples excreted by a young patient during the day is generally uncomfortable and problematic (e.g., greater possibility of sample contamination). An easier approach is a spot urine sampling. However, it should be remembered that the spot urine sample is not as representative as the round-the-clock urine samples (Kissel et al., 2005). Hence, it is recommended to collect first-morning urine because it is more concentrated, shows a longer accumulation time (approximately 8 hours) and is more representative (Barr et al., 2005; Fenske et al., 2005; Kissel et al., 2005).

Gys et. al. (Gys et al., 2020) examined the concentration of bisphenols in samples of the morning urine sampled from 7-year-old children (**Table 3**). Since BPA is an unstable pollutant that is rapidly and largely excreted in the urine, this matrix has been found to be an appropriate for assessing exposure to bisphenols in children. In the selected group, all tested bisphenols (7) were detected, with BPA, BPF and BPS showing a detection frequency of > 50%, which indicates widespread exposure. Gys et. al. (Gys et al., 2020) also assessed the trends in the concentration of bisphenols in 2012-2017. They proved that BPA concentration dropped significantly from 2012 to 2017, which is not surprising given the increasingly rigorous regulations on the use of BPA around the world. The BPF concentration remained constant over time. On the other hand, the frequency of BPB (bisphenol B) and BPS detection increased by about 10% in the studied years. The obtained results are probably related to the fact that the legal regulations cause manufacturers to move away from BPA in favour of BPA analogues. It has been shown that lower family income was associated with higher levels of BPF, and BPA measured in the urine of children. The presence of children in the smoking environment was also associated with the determination of higher BPA concentrations.

Lehmle et al., (2018) also tested the concentration of bisphenols (BPA, BPF and BPS) in urine samples collected from three study groups: adults (>20 years), teenagers (12-19 years) and children (6-11 years). All target contaminants were detected in the urine of the studied populations: BPA in 95.7%, BPS in 89.4% and BPF in 66.5% of the samples, which is consistent with the above-described results of Gys et al. (Gys et al., 2020). It was determined that the median concentration of bisphenols in children was 1.34 ng/mL for BPA, 0.27 ng/mL for BPS and 0.27 ng/mL for BPF. On the other hand, the median concentration of bisphenols in teenagers was 1.14 ng/mL for BPA, 0.30 ng/mL for BPS and 0.37 ng/mL for BPF. Children had statistically significantly higher median BPA concentrations in urine compared to adolescents. In contrast, urinary BPS and BPF levels did not differ significantly between these age groups. Lehmle et al. (Lehmle et al., 2018) also found that children from high-income families had lower levels of BPA in their urine compared to children from low-income families.

Whereas, Frederiksen et al. (Frederiksen et al., 2022) measured the concentrations of the metabolites of 15 phthalates and their two substitutes in urine from infants and their parents to

investigate possible patterns of exposure (**Table 3**). In addition, urinary analyte concentrations were considered in two separate groups: during exclusively breastfeeding and later in infancy after diet expansion, to investigate whether dietary changes altered chemicals exposure. The metabolites of 11 phthalates and both substitutes were present in 59–100% of all tested urine samples collected from infants (median concentrations in the range 0.10–5.64 ng/mL) and their parents (median concentrations in the range 0.06–18.1 ng/mL and 0.07–25.6 ng/mL for mothers and fathers, respectively). However, 9 metabolites out of 15 phthalates and both substitutes were present in >74% of all tested biological samples. The determined concentrations of phthalates and their substitutes in urine were independent of gender. Moreover, it was shown that, regardless of the type of the infant diet, exposures to most of these substances were generally of the same order of magnitude. The results of the research are quite surprising and worrying, as the use of several of the phthalates found has been legally regulated and even banned in the European Union (Frederiksen et al., 2022).

5.3. Saliva biomonitoring

In the case of the saliva biomonitoring of the chemicals, care should be taken to ensure that the sampling tools do not interfere with the analytes. Also, contamination from food or drink is a problem and attention should be paid to eliminate food and drink approximately one hour prior to saliva sampling which can sometimes be quite troublesome. Unfortunately, the common methods of saliva collection are very often unsuitable for use in very young children. For example, frequently used cotton sponges, absorbent pads, or absorbent chewing plugs may pose a choking hazard and the moment of the saliva sampling may cause discomfort to children. Literature reports indicate that the level of the contaminants in saliva may be significantly lower than the concentration of the labile chemicals in the blood, depending on the degree of the protein binding that may occur. Hence, a very sensitive analytical technique is required (Bradman and Whyatt, 2005; Morgan et al., 2011). Accordingly, Stefan-van Staden et al. (Stefan-van Staden et al., 2014) proposed three types of microsensors: stochastic microsensors, amperometric microsensors and multimode microsensors based on the stochastic and differential pulse voltammetry modes for the determination of BPA in children's saliva (**Table 3**). All the microsensors used were highly sensitive and reliable, and the results obtained were well correlated and compared with

the results obtained by the standard method (enzyme-linked immunosorbent assay, ELISA). More importantly, the authors proved that the standard method did not cover all the time the concentration ranges in which BPA is present in saliva samples, and therefore cannot be reliable for its analysis in children's saliva.

5.4. Biomonitoring of perinatal matrices

Due to the fact that exposures occurring during pregnancy are particularly worrying, as their effects on the developing fetus lead to long-term postpartum pathologies, EDCs are also determined in alternative matrices such as amniotic fluid (Shekhar et al., 2017; Wittassek et al., 2009), cord blood (Chen et al., 2017; Eick et al., 2021; Sunman et al., 2019), and placenta (Chen et al., 2017; Ruis et al., 2019). However, the sampling of these biological matrices is costly and complicated. Since the time of the delivery is not exactly predicted (apart from the scheduled caesarean section), researchers must be constantly on the phone. Also, the atmosphere in the delivery room can be hectic and tense, so there is a possibility of missing a sample. Wittassek et al. (Wittassek et al., 2009) collected amniotic fluid samples and appropriate maternal urine samples during caesarean delivery for phthalate metabolites analysis. They proved that several of the tested phthalates or their metabolites can cross the placental barrier and reach the human fetus (**Table 3**). It was observed that the concentrations of the phthalate metabolites were higher in the maternal urine samples than in the amniotic fluids. Moreover, no significant correlation was found between the concentrations of analytes in the amniotic fluid/maternal urine pairs. However, the authors admit that, due to the constant changes in the amniotic fluid, the measured levels of pollutants are not very accurate. Sunman et al. (Sunman et al., 2019) analysed cord blood samples to determine BPA, di-2-ethylhexyl phthalate and mono-2-ethylhexyl phthalate concentrations (**Table 3**). The analytes were detectable in approximately 99% of the samples (n = 100). It has been shown that exposure to the target chemical compounds in the fetal period has an adverse effect on the reproductive development of male newborns.

The abundance of hormone receptors in the placenta makes it particularly susceptible to endocrine disorders. It is also widely accepted that the placenta is a persistent organic pollutant absorber (Gingrich et al., 2020). Hence Ruis et al. (Ruis et al., 2019) quantified PBDEs in human placenta samples

from pregnant women who underwent caesarean section. The measured concentrations of the analytes in the fetal and maternal layers are presented as the ratio of the two concentrations (**Table 3**). Despite the lack of the differences in the amount of the lipids between the two tissue layers, the levels of the target compounds were higher in the fetal layers as compared to the maternal layers (2-5 times higher). The determined concentration ratios ranged from 1.2 to 5.5. The obtained results suggest that PBDEs are actively transported across the placental barrier between the mother and the fetus. If this is true, nutrients and hormones can compete for transport across the placental barrier, with potentially serious consequences for the developing fetus. Whereas, Chen et al. (Chen et al., 2017) determined the concentrations of the chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs) and PFOS in maternal serum, cord serum and placenta (**Table 3**). PFOS concentrations were higher in all tested matrices than Cl-PFESAs concentrations. It was also shown that the concentrations of the analytes decreased in the tested matrices in the following order: maternal serum > cord serum > placenta. The detection of the target chemical compounds in placenta and cord sera indicates that these analytes may be effective in transport through the placenta into the cord blood. Moreover, higher concentrations of Cl-PFESAs and PFOS in the cord serum than in the placenta suggest that these analytes can largely accumulate in the fetal cord blood.

1265 **Table 3.** Biomonitoring and analysis of endocrine disrupting compounds in biological samples coming from infant and children of early stage life.

Analytes	Type of samples	Age of children	Country	Analysis method	Concentration range	Literature
Bisphenols	Breast milk	2 weeks	Spain	LC-MS/MS	0.13-1.62 ng/mL	(Dualde et al., 2019)
Parabens					0.13-7.00 ng/mL	
Bisphenols	Breast milk	/	Poland	LC-MS/MS	2.12 to 116.22 ng/mL	(Tuzimski et al., 2020)
Bisphenols and parabens	Breast milk	2-7 weeks	Poland	LC-MS/MS	Median = 0.05-1.48 ng/mL	(Czarczyńska-Goślińska et al., 2021)
		3-4 months			Median = 0.03-0.37 ng/mL	
Perfluoroalkyl substances	Breast milk	/	Spain	HPLC-MS/MS	22-52 pg/mL	(Vela-Soria et al., 2020)
Organochlorine Pesticides	Breast milk	>7 days - >1 year	Poland	GC-MS	0-7.5 ng/g lipids	(Witczak et al., 2021)
Bisphenols	Urine	7 years	Japan	GC-MS/MS	Median = 0.07-0.89 ng/mL	(Gys et al., 2020)

Bisphenols	Urine	6-11 years	U.S.A.	HPLC-MS/MS	Median = 0.12-2.72 ng/mL	(Lehmle et al., 2018)
		12-19 years			Median = 0.13-2.30 ng/mL	
		>20 years			Median = 0.14-2.49 ng/mL	
Organophosphate esters, phenols, parabens, phthalates	Urine	3-6 years	U.S.A.	HPLC-MS/MS	Median = 0.46-57 ng/mL	(Hoffman et al., 2018)
Phthalate metabolites	Urine	3-5 years	Germany	LC/LC-MS/MS	Median = 4.6-100 ng/mL	(Becker et al., 2009)
Bisphenol A				GC-MS/MS	Median = 3.53 ng/mL	
Bisphenol A	Urine	2-5 years	U.S.A.	GC-MS	Median = 5.2 ng/mL	(Morgan et al., 2011)
Organophosphate pesticides	Urine	6 months	U.S.A.	GC-MS	GM = 45.5 nmol/L	(Eskenazi et al., 2007)
		12 months			GM = 59.5 nmol/L	
		24 months			GM = 70.9 nmol/L	
Organophosphate and synthetic pyrethroid insecticides	Urine	3 months	U.S.A.	GC-MS	Median = 5.6-13.9 ng/kg/day	(Fluegge et al., 2016)



Phthalate and substitute metabolite	Urine	7-342 days	Denmark	LC-MS/MS	Median = 0.10-5.64 ng/mL	(Frederiksen et al., 2022)
Polychlorinated biphenyls	Blood	0-11 months	Canada	HRGC	Median = 25-2142 ng/g lipids	(Verner et al., 2010)
Polychlorinated biphenyls	Serum	42 months	Germany	HRGC	Median = 1.22 ng/mL	(Walkowiak et al., 2001)
Polybrominated diphenyl ethers, poly- and perfluoroalkyl substances, poly-chlorinated biphenyls and organochlorine pesticides	Blood	0 months (birth)	Norway	/	Median = 0.03-45.13 ng/g	(Lenters et al., 2019)
		3 months			Median = 0.05-83.50 ng/g	
		6 months			Median = 0.06-108.72 ng/g	
		12 months			Median = 0.07-134.06 ng/g	
		18 months			Median = 0.07-128.47 ng/g	
		24 months			Median = 0.07-122.25 ng/g	
Bisphenol A	Saliva	4-10 years	Romania	Differential pulse voltammetry and	10-880 ng/mL	(Stefan-van Staden et al., 2014)

					stochastic measurements	
Phthalate metabolites	Amniotic fluid	0 months	Germany	LC-MS/MS	Median = 0.53-7.8 ng/mL	(Wittassek et al., 2009)
Phenols	Amniotic fluid	0 months	India	GC-MS	Median = 0.94-21.41 ng/mL	(Shekhar et al., 2017)
Bisphenol A	Cord blood	0 months	Turkey	HPLC	Median = 4.77 ng/mL	(Sunman et al., 2019)
Phthalates					Median = 0.13-0.29 ng/mL	
Poly- and perfluoroalkyl substances	Cord blood	0 months	U.S.A.	LC-MS/MS	GM = 0.1-2.0 ng/mL	(Eick et al., 2021)
Polybrominated diphenyl ethers				GC-HRMS	GM = 2.2-10.7 ng/mL	
Polybrominated diphenyl ethers	Placenta	0 months	U.S.A.	GC-MS	Ratio of analytes in fetal vs maternal placentas = 1.2- 5.5	(Ruis et al., 2019)



Chlorinated polyfluoroalkyl ether sulfonic acids	Cord serum				Median = 0.01-0.60 ng/mL
Perfluorooctane sulfonate					Median = 3.64 ng/mL
	0 months	China	UPLC-MS/MS	(Chen et al., 2017)	
Chlorinated polyfluoroalkyl ether sulfonic acids	Placenta				Median = 0-0.34 ng/mL
Perfluorooctane sulfonate					Median = 0.35 ng/mL

- 1266 GC-MS - gas chromatography coupled with mass spectrometry, GC-MS/MS - gas chromatography coupled with tandem mass spectrometry, HPLC-MS/MS - high performance liquid chromatography coupled with tandem mass spectrometry, UPLC-
- 1267 MS/MS – ultra high performance liquid chromatography coupled with tandem mass spectrometry LC-MS/MS - liquid chromatography coupled with tandem mass spectrometry, LC/LC-MS/MS - multidimensional liquid chromatography coupled with
- 1268 tandem mass spectrometry, HRGC - high resolution gas chromatography, HPLC - high performance liquid chromatography, GC-HRMS - gas chromatography coupled with high resolution mass spectrometry, GM – geometric mean, U.S.A. - United
- 1269 States of America

6. Avoiding harmful chemicals in baby products: advices

Every parent instinctively cares about the welfare of the child. Sometimes, however, a lack of knowledge and awareness can cause them to make the wrong choices. Chemicals are all around us, found in everyday products. Babies and young children are exposed to chemicals through various routes including inhalation, ingestion or absorption through the skin.

Children in order to develop properly need to explore the surrounding world with all the senses. They play with different surfaces by touching it or putting an item in the mouth, therefore, all objects that are accessible to the youngest in everyday life need to be safe, free of harmful chemicals.

Babies and children can be exposed to harmful chemicals in products in widespread use, such as food, and food packaging, cosmetics, toys, clothes, baby bottles and all the items used in a baby room such as furniture, paint, mattresses or cribs, not to mention products not designed for kids but in their closest vicinity. Children are particularly vulnerable as they are still developing, thus parents need to be aware of the steps that need be taken to reduce baby's risk of exposure to harmful chemicals, including endocrine disruptors.

There are three basic principles (Time, Product, Alternative) that are important to remember when making decisions about how to organise the daily lives of children.

1. Giving a time: the baby's space, shopping, preparing meals should be planning Good, conscious decisions take time.

2. Reading the composition of products: looking for products intended exclusively for children and bearing the EU label; looking for products with an Ecolabel which certifies products with a guaranteed, independently-verified low environmental impact. Remembering which chemicals to avoid!

3. Looking for alternatives: the possibility of using greener substitutes, made of natural, non-toxic materials should be checked. The less intense the smell and colours, the better.

Table 4 summarizes some bullet points summarising the most basic tips for parents.

Table 4. Information on some bullet points summarising the most basic tips for parents

Aspect	Advices	Alternatives
Home	<p>Steps that you can take to limit the exposure to harmful chemicals, including endocrine disruptors, while preparing your home for your baby:</p> <ul style="list-style-type: none"> • renovate at least 3 months before the due date, ventilate your home well afterwards; • choose water-based, solvent-free and low-emission products; • use non-toxic mattresses and cribs with the EU Ecolabel (these are not treated with the most toxic flame retardants); • air any new mattresses thoroughly before sleeping on them; • consider an alternative flooring such as solid wood, cork, tile or natural linoleum as carpets may contain hazardous chemicals. 	
Food	<p>You can reduce your and your child's risk of exposure to EDCs in foods by:</p> <ul style="list-style-type: none"> • reducing your consumption of meat and dairy products, opting for organic food, and avoiding fast food; • choosing fish lower down the food chain, such as sardines or anchovies as larger fish higher up the food chain eat smaller fish (bioaccumulation); • limiting intake of certain species of fish (long-lived and higher up the food chain species – such as shark, 	<p>Try to choose:</p> <ul style="list-style-type: none"> • baby bottles that are free from all bisphenols. Choose BPA-free • stainless steel water bottles and food containers (for example for

	swordfish, pike, tuna, hake, tilefish and king mackerel (“Avoiding harmful chemicals in baby products: advice for parents,” n.d.).	children’s school lunches) • fruit and vegetables
Food preparation process	To limit the risk of exposure to harmful chemicals: <ul style="list-style-type: none"> • choose a stainless steel or glass reusable cup; • don’t microwave food in plastic packaging; • avoid black plastic cooking utensils; • avoid non-stick pans. 	loose • food in glass jars • take-aways reduction.(“Avoiding harmful chemicals in baby products: advice for parents,” n.d.)
Food packaging	Avoid: <ul style="list-style-type: none"> • plastic bottles; • plastic food wrap; • packaging with greaseproof lining; • canned foods; • take-away and fast-food containers; • packaging labelled with recycling codes 3 and 7. 	
Personal care products	Try to: <ul style="list-style-type: none"> • choose non-toxic baby care products such as shampoos, moisturisers, creams, soaps or nappies by reading a label, if possible pick those with an ecolabel; • avoid parabens, triclosan and chemicals with ‘fluoro’ in the name or ‘PTFE’; • look for paraben-free baby shampoo and soap; • select fragrance-free, organic cotton and reusable nappies with an ecolabel. 	

Toys	<p>Toys are regulated under the Toy Safety Directive in the EU. Try to:</p> <ul style="list-style-type: none"> • reduce the risk of the toys containing harmful chemicals; • buy toys from trustworthy shops and online stores; • avoid toys that smell strongly of chemicals or are heavily scented; • avoid soft plastic toys, as they may contain endocrine disruptors like phthalates; • choose free from lead, and non-toxic if it is painted, and make sure it is meant for children. 	
Clothes	<p>To avoid exposure to endocrine disruptors:</p> <ul style="list-style-type: none"> • read a label to avoid PFAS (or an old name PFC); • buy garments labelled PFAS-free or PFC-free; • use alternatives. 	<p>Some yarns used in homemade baby clothes, in order to be more durable or washable, may contain plastic as they are mixed with acrylic or nylon fibres. Wool could be a natural alternative as it do not contain plastics. Moreover, untreated wool has more advantages, it is naturally flame retardant and water repellent.</p>

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.297 **7. Summary**

The fetus, infant, and child are widely exposed to chemicals with known or suspected endocrine disrupting effects and given increasing evidence of links to adverse effects in their life, research on EDCs is urgently needed. In the present article, a comprehensive literature survey was performed in order to provide an overview on the exposure of infants to EDCs and insights on the uptake, the mechanisms of action and biotransformation in baby/human body. In addition, detection and chemical identification methods were discussed in view of the relevant literature.

Based on the published data it is evident that EDCs have been routinely detected in trace amounts in different biological samples creating global concern over their potential adverse effects. Despite biomonitoring studies documenting that infants are exposed to dozens of potential EDCs across the lifespan and that some EDC exposures are correlated with each other, most of the studies are focused on the effects on single compounds and there is a lack of research on health effects of EDC mixtures. There is also much less information on the risks of chronic, low dose exposure of these compounds to infants. Based on this, monitoring in biological samples is almost certain to continue, in the ongoing studies of EDCs occurrence and toxicity.

Existing regulatory frameworks actions are not sufficient to address EDCs concerns on infants. This is due partly to the huge number of compounds that can be classed as EDCs. Hence, as research continues, anxious parents can take preventive measures to diminish infants' exposure to EDCs.

Considering all of the information mentioned in this publication, it is essential to bear in mind what is already known about EDCs and to deepen our knowledge to establish rules of conduct aimed at limiting exposure to EDCs' negative effects. We need to be aware that there is plenty of evidence showing that exposure to EDCs may adversely impact the health of adults and children through altered endocrine function—suggesting their link to endocrinopathies. In addition, we also need to remember about the environment. As the ECDs are release to the environment from various products and some of ECDs are slow to break-down in the environment, we should be aware how important is to choose the proper goods which are in use in our daily life. This is the reason why gaining knowledge about EDCs and their impact on human health as well as environment is of high importance.

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