Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Review paper | Praca poglądowa
Pediatr Endocrinol Diabetes Metab 2018;24,2:88-95
DOI: 10.18544/PEDM-24.02.0107

Endocrine disruptor compounds in environment: As a danger for children health

Związki endokrynnie czynne w środowisku – jako zagrożenie dla zdrowia dzieci

[1]Monika Beszterda, [2]Rafał Frański

[1]Poznań University of Life Sciences, Faculty of Food Science and Nutrition, Department of Food Biochemistry and Analysis, [2]Adam Mickiewicz University in Poznań, Faculty of Chemistry, Department of Supramolecular Chemistry
[1]Uniwersytet Przyrodniczy w Poznaniu, Wydział Nauk o Żywności i Żywieniu, Katedra Biochemii i Analizy Żywności, [2]Uniwersytet im. Adama Mickiewicza w Poznaniu, Wydział Chemii, Zakład Chemii Supramolekularnej

Abstract
Endocrine disrupting compounds (EDCs) are heterogenous in structure and include synthetic organic compounds such as pharmaceutical agents, plant protection products, plastics, plasticizers, polychlorinated biphenyls, dioxins, flame-retardants, and antifoulant paint additive, as well, as natural plant-derived EDCs termed phytoestrogens and mycoestrogens. Children and adults are exposed daily to EDCs during drinking contaminated water, eating, breathing polluted air or direct contact with chemicals. Prenatal and perinatal period, infancy, childhood, and puberty are critical time of development during which maturing systems are particularly sensitive to hormonal disruptions (small elimination of xenobiotics). Exposure to environmental chemicals with estrogenic or anti-androgenic action may disrupt female reproductive tract development, also testosterone synthesis and sexual differentiation, leading to adult testis dysfunction and infertility. What is important, today there is still no definitive risk assessment tool for EDCs.
Key words
endocrine disrupting chemicals, persistent organic pollutants, reproductive system, obesogens

Streszczenie
Związki endokrynnie aktywne (ang. endocrine disrupting chemicals, EDCs) stanowią grupę syntetycznych organicznych związków o zróżnicowanej strukturze chemicznej, do których zaliczamy m.in.: wybrane farmaceutyki, środki ochrony roślin, tworzywa sztuczne, plastyfikatory, polichlorowane bifenyle, dioksyny, środki opóźniające palność, dodatki do farb czy związki pochodzenia naturalnego, takie jak fito- i mykoestrogeny. Podlegamy codziennej ekspozycji na EDCs podczas konsumpcji skażonej wody i żywności, oddychania zanieczyszczonym powietrzem lub poprzez bezpośredni kontakt z substancją aktywną. Jednakże okres pre- i perinatalny, niemowlęctwo, dzieciństwo oraz pokwitanie należą do krytycznych okresów rozwoju, podczas których podatność na wystąpienie zaburzeń hormonalnych pod wpływem bodźców chemicznych jest wysoka (niska eliminacja ksenobiotyków z ustroju). Narażenie na środowiskowe kontaminanty wykazujące działanie estrogenne lub anty-androgenne może zaburzać prawidłowy rozwój żeńskiego układu rozrodczego, syntezę testosteronu i proces różnicowania płciowego, co prowadzić może do dysfunkcji jąder i rozwoju niepłodności u osób dorosłych. Dotychczas nie opracowano jeszcze skutecznych narzędzi do oceny ryzyka wywołanego obecnością EDCs w środowisku.
Słowa kluczowe
związki endokrynnie aktywne, trwałe zanieczyszczenia organiczne, układ rozrodczy, obesogeny

dr inż. Monika Beszterda
Uniwersytet Przyrodniczy w Poznaniu Katedra Biochemii i Analizy Żywności, 60-623 Poznań, ul. Mazowiecka 48
tel: 61/848-73-50, monika.beszterda@up.poznan.pl

Received: 19.04.2018
Accepted: 20.05.2018
Conflict of interests: none declared.

Pediatr Endocrinol Diabetes Metab 2018;24,2:88-95

Introduction

Endocrine disrupting chemicals (EDCs) are substances that can affect processes associated with the endocrine system and alter its functioning by interfere with endogenous steroids such as estrogen, anti-androgen and androgen, as well as other hormone activity. As EDCs are ubiquitous in today's world, subchronic and chronic exposure at low doses over lifetime is common. Cumulative EDCs exposure from a different routes can approach or exceed so-called „safe" doses complicating efforts to establish a discrete exposure level for use in risk assessment [1].

According to the Fourth National Report on Human Exposure to Environmental Chemicals, nearly all Americans in every age group (6 years or older) have detectable concentration of bisphenol A, phthalate metabolites, triclosan, and other widespread EDCs in their urine. The current recommendations by scientific organizations, including: the World Health Organization and the United Nations Environment Program, the Endocrine Society and the American Academy of Pediatrics, recomended minimizing exposures to endocrine disrupting chemicals [2]. Also the Polish Society of Endocrinology points out the harmful health effects caused by EDCs commonly applied in daily life as food contaminants, food and beverages containers, components of plastics, pharmaceuticals and cosmetics [3]. The ascertainment is based on the alarming data about the increase of the frequency of endocrine disorders occurrence such as: precocious puberty in girls and boys, genital malformations, endometriosis, polycystic ovary syndrome, obesity, diabetes and hormone-dependent cancers (endometrium, ovaries, breast, testicles). According to the interpretation of the Expert Panel [4], EDCs can contribute substantially to male reproductive disorders and diseases, with nearly €15 billion annual associated costs in the European Union.

Prenatal and perinatal period, infancy, childhood, and puberty are critical time of development during which maturing systems are particularly sensitive to hormonal disruptions (small elimination of xenobiotics) [2]. EDCs have been found in materials intended for use by infants such as toys, teethers, flame retardant pajamas and baby bottles, as well as in food, (soy-based) infant formula, breast milk and also in polluted environment. Toddlers have higher exposure to chemicals due to higher metabolic rates; more ingestion of food, drink and air per unit of body weight compared to adults; more frequent object-to-mouth and hand-to-mouth activity; and high rates of development susceptible to environmental contaminants [1]. Moreover infants and children often are exposed to consumer products that are not specifically dedicated for children (e.g., toothpaste, body wash, lotion and conditioner). Children have physiologically thinner skin than adults and also have greater skin surface area per unit of body weight, which may lead to greater exposures to triclosan, parabens and phthalates belonging to EDCs [2].

Due to the above the purpose of this article is to provide a brief overview of common EDCs, also short description of their mechanisms of action with attempts to assessment potential effects of EDCs on child development and health.

Characteristic of the selected EDCs

EDCs are heterogenous in structure and include synthetic organic compounds such as pharmaceutical agents, pesticides (e.g. organophosphates, dichloro-diphenyl-trichloroethane, methoxychlor), fungicides (vinclozolin), plastics, plasticizers, polychlorinated biphenyls, dioxins, flame-retardant polybrominated diphenyl ether, and antifoulant paint additive (tributyltin), as well as natural plant-derived EDCs termed phytoestrogens and mycoestrogens [5]. A number of estrogenic chemicals are phenolics, include simple phenols, phenolic acids/phenolic aldehydes, acetophenones, phenylpropenes, bisphenols, benzophenones, anthraquinones, tyrosine derivatives, phenylacetic acids, hydroxycinnamic acids, coumarins/isocoumarins/chromones, naphthoquinones, stilbenes/stilbenoids, chalcones/chalconoids, flavones/flavonoids, flavolans, lignans/neolignans, and diarylheptanoids. Notwithstanding, chemicals without a phenolic moiety may also demonstrate estrogenic activity, include anilines, carboranes, indoles, metalloestrogens, perfluorinated compounds, phthalates, polycyclic aromatic hydrocarbons and terpenes/terpenoids (monoterpenes, diterpenes, triterpenes, tetraterpenes, sesquiterpenes, sterols, steroids, saponins and meroterpenes) [6]. Summarizing, human are exposed daily to EDCs during drinking contaminated water, eating, breathing polluted air or direct contact with chemicals. Below, the main group of EDCs have been short characterized.

Phytoestrogens

Phytoestrogens are naturally occurring plant compounds found in numerous vegetables and fruits categorized into three classes: the isoflavones, coumestans and lignans. Genistein, daidzein, biochanin A and glycitein are the predominant isoflavones found in soybeans and make up the most important dietary source of plant-derived estrogens for humans [5]. It is relevant to note that the relative binding affinities of these compounds for both estrogen receptors (ER) are far greater than for many of the synthetic EDCs of concern, such as bisphenol A, DDT, methoxychlor or nonylphenol [7].

The total isoflavone content is high in soy flour (150-170 mg 100 g^{-1}), soy protein isolate (91 mg 100 g^{-1}), fermented bean – natto (82 mg 100 g^{-1}) but significantly lower in tofu (25-30 mg 100 g^{-1}) or soymilk (1-3 mg 100 g^{-1}) [5]. What is lately controversial, soy-based infant foods (based on soy protein isolate), have been used not only for feeding infants showing symptoms of cow's milk allergy and lactose intolerance [8]. As indicates Cederroth and coworkers [5] the circulating concentration of phytoestrogens in infants fed with soy formula may be up to 13,000 times higher than the endogenous estrogen contents, or 50-100 times higher than the estradiol concetration, present in pregnant women.

Phthalates

Phthalates are a group of chemicals used to make plastics more flexible and currently, also used as solubilizing or stabilizing agents. Low molecular weight phthalates are found in personal care products (perfumes, lotions, cosmetics) due to the fact they help to dissolve ingredients in the product, certain dietary supplements and medications, and other consumer goods [6,9]. High molecular weight phthalates are found in flexible polyvinyl chloride (PVC) food packaging, home furnishings and other building materials [6]. Six types of these chemicals are banned from children's toys. They are non-covalently bonded to their parent materials and can easily leach into the environment and be ingested, inhaled, or dermally absorbed [2,10].

Triclosan

Triclosan (5-chloro-[2,4-dichlorophenoxy] phenol), a commonly used as antibacterial agent, is widely found in antibacterial soaps, shampoo, body washes, toothpaste, toothbrushes, laundry detergents, kitchen cutting boards, textile goods, plastics in furniture, sporting equipment, and toys [2,11]. It is a synthetic, lipid-soluble compounds contains two phenol functional groups, indicating its endocrine potential. Additionally, the structure of triclosan closely resembles anthropogenic estrogens as well as estrogenic and androgenic EDCs. It has been detected in different biological samples, including blood, human milk and urine, among which urinary detection has been frequently used in human exposure assessment [11].

Bisphenol A and similar congeners

Bisphenol A is a chemical found in polycarbonate beverage containers and bottles, linings of canned foods and beverages, epoxy resins, medical equipment, dental sealants and thermal papers, which are applied to make receipts from stores. What is particularly important, bisphenols are ubiquitous and have been identified in nearly all urine samples of adults and children, also in breast milk, placental tissue, and human fetal liver [6, 10]. Bisphenol A and congeners are known to have structural similarity to estradiol and binds to estrogen receptor α with relatively low affinity. They may interfere with androgen receptors as well as thyroid receptors. Based on animal and epidemiological studies, bisphenol A is one of the EDCs that can support development of obesity and type 2 diabetes [2].

Parabens

Parabens are antibacterial agents used as preservatives in personal care products, including skin lotions, make-up products, perfumes, clothing, car seats, mattresses, and carpet padding. It is estimated that around 40% of rinse-off personal care products and 60% of leave-on products comprise parabens. Exposures to parabens may pose potential health threat because of evidence of weak estrogenic and anti-androgenic activity during*in vitro* and rat experiments. In humans, parabens are known to be readily absorbed through surface of the skin, and this application has been shown to increase urinary parabens contents. However specific health effects of parabens in humans are not clear and further investigation is needed [2,12].

Persistent organic pollutants

Persistent organic pollutants are lipophilic and stable chemicals with long half-lives that bioaccumulate up the food chain, and include polychloroinated biphenyls, polybrominated diphenyl ethers, organochlorine pesticides (such as DDT, chlordane and hexachlorobenzene), among others [13]. Persistent organic pollutants have been associated with a wide range adverse health effects, because they can accumulate in white adipose tissue and may cause male and female reproductive problems, thyroid effects, obesity, diabetes, and endocrine-related cancers. Polybrominated diphenyl ethers have also been classified as developmental neurotoxicants based on the results of experimental and observational research [14–16], such as prenatal exposure was associated with more attention problems at ages 3, 4 and 7 years [17]. Individuals can be exposed through consumption of foods with a high fat component, such as: fatty fish, meats, eggs, plant oils, beside during consuming water, and contact with contaminated soil [18]. Besides diet, house dust has been recognized as an important exposure media for polybrominated diphenyl ethers and in Frederiksen and coworkers study [19] amount of these compounds in human milk samples were significantly correlated with dust levels. Results of research on eighty-three children aged 12-36 months also showed that playing with plastic toys was associated with higher handwipe levels of polybrominated diphenyl ethers, while frequent vacuuming decreased their handwipe levels [20].

Mixture

Human exposure is never limited to one chemical, but includes a mixture of different EDCs and other environmental pollutants of various origins, which can have additive or synergistic effects [5, 21]. *In vitro* experiments have indicate that low concentrations of genistein, nonylphenol and 8-pre-nylnaringenin were more effective when applied in combinations, rather than alone, in causing detrimental effects on the key processes of capacitation and acrosome reaction both in mouse and human spermatozoa [22]. Christiansen and coworkers in turn [23] demonstrated that a combined administration of anti-androgenic chemicals (flutamide, procymidone, vinclozolin) at doses where each of the individual chemicals caused no observable effects, resulted in significant impairment of masculinization, such as increased frequency of hypospadias in the male offspring.

Mechanisms of action

One of the main reasons why a number of new signaling pathways associated with EDCs were recognized lately is the availability of a diversity of new technologies to detect estrogenic chemicals. Estrogenic signal networks can be categorized into

Pediatr Endocrinol Diabetes Metab 2018;24,2:88-95

two types: intracellular and extracellular. The genomic pathway, which engages transcription of target genes, and the non-genomic pathway, which rapidly transduces signals mediated by membrane-bound estrogen receptors (ERs) and other receptors through bypassing or/and crosstalk, belong to the former, whereas the pathways of paracrine or/and autocrine signaling, which involve different hormones, cytokines and growth factors, belong to the latter [1,6].

Mechanism of EDCs action mainly include direct mimicry of sex steroids or morphogens and interference with epigenomic sculpting over differentiation of cell and tissues. It is possible because EDCs can bind both estrogen receptors (ER): α and β, and mimic estrogenic actions. In addition, recent studies have revealed the presence of other ERs, such as the estrogen-related receptors (ERRs), variants of ERα or ERβ (ER-X and ER-α36) and uncharacterized ERs with which EDCs can also interact [6].

The estrogenic activity of EDCs may in fact depend of the inherence or/and recruitment of co-activator or co-repressor proteins present in specified cell types or tissues at specific times of development. Plant estrogens act either by initiating transcription via a classical mode of action involving the interaction between nuclear ERs and estrogen response elements (EREs), or by non-genomic effects mediated by cytoplasmic or membrane-associated ERs. The non-genomic effects mediated by ERs commonly involve rapid cellular responses leading to calcium flux, nitric oxide release, and/or activation of various signaling pathways, such as the mitogen-activated protein kinase (MAPK), AMP-activated protein kinase (AMPK), and phosphoinositide 3 – kinase (PI3K) pathways, as observed in different cell lines [5,24]. Frequently, these chemicals act alongside or in place of endogenous chemicals. To complicate matters, sometimes there is no effect at high concentrations but adversity at low concentrations, as well as vice versa [1].

Role of EDCs in the development of selected disorders – evidence from human studies

Currently, we do not have a complete understanding of EDCs and their effects on the human body, because our understanding of the specific health effects is based on animal model studies as well as epidemiological studies [2]. These group of compounds have complex modes of action with multiple components that manifest exeptionally within a given species and the effect an EDCs on various species may differ. This makes it difficult to extrapolate information between levels of organization, or from one species to another. Besides as with another developmental and reproductive toxins, there are cases in which timing of the dose is more important than the dose size since sensitivity to exposure is heightened during critical developmental periods [1].

The principle that the nutritional, metabolic, and hormonal environment afforded by the mother can constantly program the structure and physiology of her offspring was established long ago [25]. There is evidence that embryonic, fetal, and neonatal tissues could interpret estrogens and EDCs in a different way – or by different mechanisms – than tissues of adult [26]. Fetal exposure to environmental chemicals with estrogenic or anti-androgenic action may disrupt female reproductive tract development, also testosterone synthesis and sexual differentiation, leading to adult testis dysfunction and infertility [27].

Effects on the reproductive and endocrine system

The etiology of testicular dysgenesis syndrome – a group of male reproductive system disorders, including hypospadias, undescended testes, low sperm counts, and testicular cancer – is well understood and multifactorial involving genetic component and a potential environmental exposure. Phthalates are group of chemicals that have been implicated in male reproductive health as hypospadias and cryptorchidism cases [2]. In two studies of male infants in the United States (n=106) and Japan (n=111), mothers who had higher concentrations of phthalate metabolites during pregnancy were more likely to have infant boys with an incomplete testicular descent, reduced penile size and reduced anogenital distance, which is a marker for insufficient fetal androgenization and is associated with a higher risk of testicular dysgenesis conditions [28,29]. Respectively, a Danish study reported significant decreases of free testosterone in blood serum, higher serum sex hormone binding globulin (SHBG) levels and luteinizing hormone (LH):free testosterone ratios (hormones related to Leydig cell function) in 3 month-old boys in relation to phthalates in maternal breast milk [30]. It is suspected that prenatal exposure to di-2-ethylhexyl phthalate, butyl-benzyl phthalate, di-n-butyl phthalate, and di-iso-butyl phthalate reduces Leydig cell testosterone production by decreasing the expression of genes involved in cholesterol biosynthesis and steroidogenic enzymatic pathways [10]. In turn, case-control study reported increased risk of hypospadias and cryptorchidism in relation to parental occupational exposure to pesticides, although the number of cases in the study was relatively small (14 cases of hypospadia, 18 of cryptorchidism) [31].

There are also some inconsistent evidences for reduced birth weight in association with exposure to persistent organic pollutants, organophosphate insecticides, and triazine herbicides. A meta-analysis of women (n=8,000) from twelve European birth cohorts dating back to 1990 reported significant losses in birth weight in relation to markers of low-level exposure to polychlorinated biphenyls, but not DDT [13]. A small case-control study taking place in Mexico City (n=60) showed higher concentrations of phthalates and bisphenol A in third trimester urine of women who delivered preterm in comparision to women who delivered at term [32]. On the other hand, few studies have reported void or even positive associations between phthalates and gestation length [33].

Increased frequency of precocious puberty are considered to be a significant public health concern because it is a risk factor for endocrine-related diseases after reaching maturity. Several studies have noticed an association between exposure

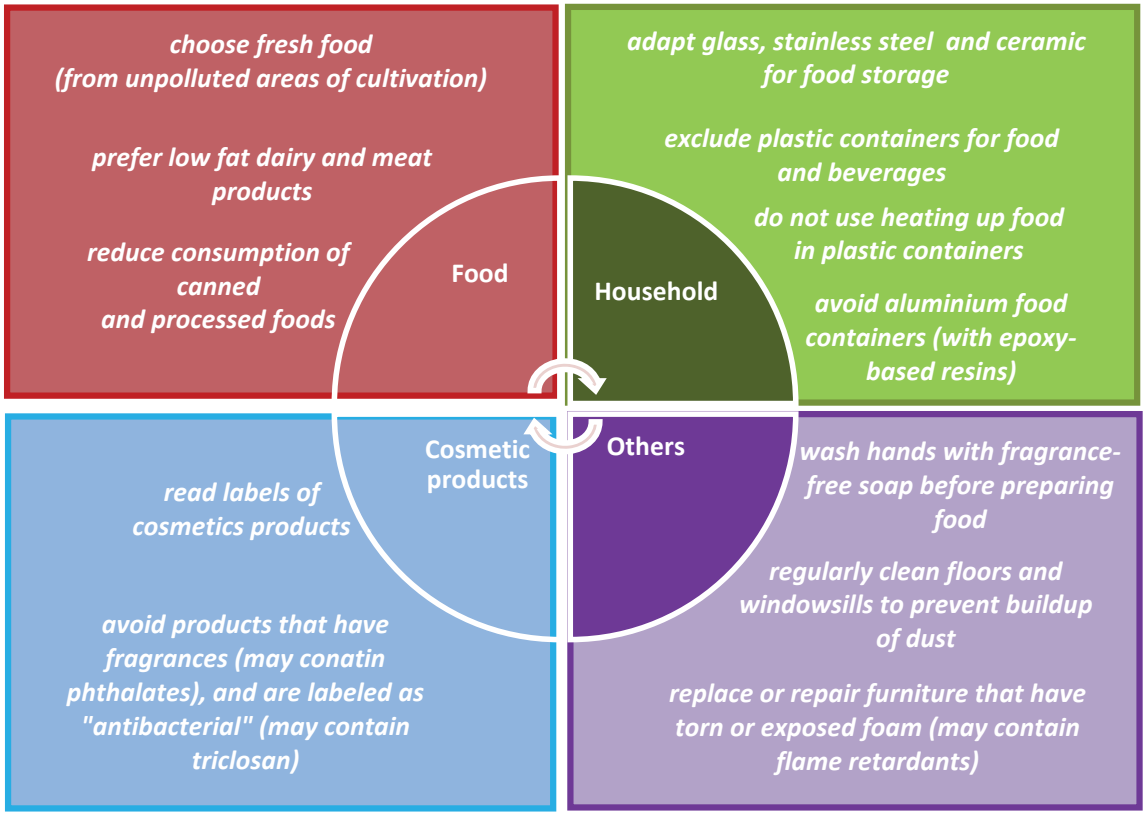

Fig. 1. Selected strategies to reduce exposures children to EDCs
Ryc. 1. *Wybrane strategie zmniejszania narażenia dzieci na działanie EDCs*

to persistent organic pollutants and precocious puberty or earlier menarche in girls, and delayed puberty in boys [34,35, 36]. However, there have also been a number of research that have not reported these relationships [37, 38, 39]. A recent cross-sectional study noted a higher prevalence of breast buds during the second year of life in female infants fed soy-based formula, in comparision to their breast or cow-based formula fed counterparts [5, 40]. The single research to date with positive results evaluated triclosan levels in spot urine among girls (n=1151) aged 6-8 years and analyzed the relations of triclosan exposure with breast and pubic hair growth. Triclosan showed a small inverse association with pubic hair stage, indicating potential dependency between triclosan exposure and pubertal development [11, 41]. In Wolff and coworkers [6] prospective study about pubertal development among girls (n=1239, 6-8 years old) recruited at three U.S. sites, four phenols were found to be associated with begining of puberty. For enterolactone and benzophenone-3, girls experienced breast development 5-6 month later, while earlier breast development was seen for triclosan and 2,5-dichlorophenol. A small study carried out in Turkey reported that concentrations of high molecular weight phthalates in plasma samples were significantly higher in 11 to 15 year olds boys with pubertal gynecomastia in comparision to a control group [9]. Recently, a large study involving women (n=19,972) found that an increased risk of developing benign smooth-muscle tumors of the uterus (uterine leiomyomata or fibroids) is associated with feeding soy-based formula during infancy [5, 42].

Besides, both human and animal studies suggest that polychlorinated biphenyls, polybrominated diphenyl ethers, pesticides, phthalates, and bisphenol A, in addition to numerous other EDCs, could disrupt thyroid signaling *via* diverse mechanisms.Three European mother-child cohorts (Belgium, Norway, Slovakia; n=1,784) were pooled for the purpose to determine early-life exposure to EDCs based on samples of cord plasma and/or breast milk [43]. As a result, polychlorinated biphenyls and DDE impacts newborn thyroid-stimulating hormone (TSH): higher exposure levels were associated with 12-15% lower TSH levels. As indicates Poppe and Glinoer [44] maternal hypothyroidism during pregnancy causes preterm birth and low birth weight, and it impairs post-natal mental development in infants. EDCs potentially alter human thyroid function during pregnancy by inhibiting thyroglobulin iodination, inhibiting iodide transport, or competitively inhibiting thyroid hormone binding receptors [45]. Moreover, in Huang and coworkers study [45], levels of

Pediatr Endocrinol Diabetes Metab 2018;24,2:88-95

T4 and FT4 in pregnant women were significantly negatively associated with urinary phthalate levels after adjusting for gestation time, age and BMI. As indicates these authors, the fall in T4 and FT4 levels during pregnancy can be potentially harmful to fetal development.

Metabolic disorders

The prevalence of overweight and obesity is rapidly increasing worldwide. In addition to diet, physical activity and genetics, environmental "obesogens" – chemicals that inappropriately alter lipid homeostasis to promote adipogenesis and lipid accumulation – may play a key role in these trends [13]. According to the "environmental obesogen hypothesis", early-life (including *in utero*) exposure to EDCs may disturb the mechanisms engaged in adipogenesis or energy storage, and thus may increase the susceptibility to overweight and obesity. Epidemiological studies indicate that pre – and early postnatal exposure to some EDCs may increase the risk of these disorders during childhood. Among EDCs a persistent organic pollutants were the most studied substances between early-life exposures that can be obesogenic [46]. Example, cord blood polychlorinated biphenyls concentrations were associated with increased BMI or alteration in BMI from ages 1 to 3 in a Belgian prospective study [13]. Also prenatal hexachlorobenzene exposure has been positively associated with rapid growth in the first 6 months of life and obesity in infancy and childhood [47].

The most recent study noticed likewise that higher bisphenol A contents in children's urine were associated with increased BMI z-score at 4 years of age, where prenatal bisphenol A levels were negatively associated with BMI and adiposity measures in girls and positively in boys [48]. Also low-molecular weight phthalates exposure in girls aged 6–8 years was positively associated with changes in BMI and waist circumference after several years [49].

Effects on the neurobehavioral development

Neurodevelopmental disorders are prevalent worldwide, with evidence that rates of certain disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) have been increasing in recent decades and there is growing evidence that exposure to EDCs may play a significant role [13]. Longitudinal and cross-sectional human studies have associated exposure to EDCs (polychlorinated biphenyls, pesticides), both *in utero* and during early childhood, and neurodevelopmental disorders such as decreased IQ, poorer memory, ASD, ADHD, and other behavioral problems. One hypothesis that has been advanced to account for the cognitive style in ASD, is referred to as 'the extreme male brain' as resulting from growing testosterone exposure *in utero*. According to Kim and coworkers [50] EDCs are positively associated with symptoms of attention deficit hyperactivity disorder (ADHD) in children, also air-born phthalates indoors at the time of conception were corelated to an increased risk for autism spectrum disorder (ASD) in the offspring [51]. There is also recent evidence that various phthalates may be associated with decreased masculine play in boys, gestational exposure to polybrominated diphenyl ethers – with lower scores on tests of mental development in the first years of life, and gestational exposure to bisphenol A – with poorer executive function and behavior in 3 year-old girls [13]. Moreover phthalate exposure during pregnancy has been related to changes in expected behaviors of infants, and have been linked to an occurrence of asthma disease development risk. Children who had elevated maternal cord blood content of polybrominated diphenyl ethers scored lower on mental and physical development tests at ages 12-48 and 72 months [2]. Also epidemiological studies have found that prenatal exposure to bisphenol A was related to effects on neurobehavioral development. Elevated contents of bisphenol A during pregnancy were associated with increased internalizing problems and increased symptoms of aggressive behaviour, anxiety, and depression and among boys at 7 years of age [2].

Prevention strategies to decrease exposures to EDCs

Summarizing, increased exposure to EDCs may occure through specific routes that are unique to children (transplacental, breast milk, infant formula), also through ingestion, inhalation, or dermal absorption and during critical development periods (prenatal development, infancy, childhood, puberty). Exposure to the EDCs occurs among everyone as they go about their normal activities, as well all parents and health care representatives could be advised to take certain steps in an effort to reduce exposure (Fig. 1). Simultaneously individual exposure scenarios depend on many factors, many of which are not modifiable through personal activities and choices.

Among fresh foods, exchanging a diet of conventional produce with organic produce can significantly minimize exposure to organophosphate pesticides for children who are exposed mainly through residues in food. Similarly, replacing highly processed food with unprocessed, may limit absorption of toxic substances which arise during high-temperature machining (such as polycylic aromatic hydrocarbons). Respectively, for high molecular weight phthalates and bisphenol A, replacing foods in the diet that involve plastic food packaging with "fresh" alternatives can decrease exposure by over 50%.

Parents can purchase consumer goods (toys, bottles, soothers) or personal care products labeled phthalate-free or bisphenol A-free, which are becoming more widely available. However, this trend is primarily due to marketing purposes and alternative substances that are used as replacements, like bisphenol S and bisphenol F also demostrate endocrine disrupting activity. Since interiors of houses, offices and cars still have many products that include polybrominated diphenyl eters and other flame retardants, also careful product selection and cleaning practices to decrease indoor dust exposure can help minimize exposure [2,13].

Conclusions

The trends of endocrine-related diseases in children and adulthood cannot be fully explained by known predictors (living conditions, BMI), and exposure to EDCs have been hypothesized to be a significant contributor. The exposure profile for EDCs is extensive and complicated as wealth of anthropogenic sources include: pharmaceutical, industrial, domestic and agricultural applications. Simultaneously, contact with multiple EDCs that have similar targets my result in combined exposure that poses a threat to health where individual exposures do not [1,13]. *Ipso facto*, it took many years for the health disorders of EDCs to be recognized and regulatory responses considered because their most devastating effects are ordinarily manifested only generations later, in the offspring of those exposed. To accommodate the temporal dimensions of EDC exposure, multigenerational research would need to explore a range of dosage levels at different life stages.

References

1. Fuhrman VF, Tal A, Arnon S. *Why endocrine disrupting chemicals (EDCs) challenge traditional risk assessment and how to respond*. J Hazard Mater. 2015;286:589-611.
2. Wong KH, Durrani TS. *Exposure to endocrine disrupting chemicals in consumer products – a guide for pediatricians*. Curr Probl Pediatr Adolesc Health Care 2017;47:107-118.
3. Rutkowska A, Rachoń D, Milewicz A et al. *Polish Society of Endocrinology Position statement on endocrine disrupting chemicals (EDCs)*. Endokrynol Pol. 2015;66:276-285.
4. Hauser R, Skakkebaek NE, Hass U et al. *Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union*. J Clin Endocrinol Metab. 2015; 100:1267-1277.
5. Cederroth CR, Zimmermann C, Nef S. *Soy, phytoestrogens and their impact on reproductive health*. Mol Cell Endocrinol. 2012;355: 192-200.
6. Wolff MS, Teitelbaum SL, McGovern K et al. *Environmental phenols and pubertal development in girls*. Environ Internat. 2015;84: 174-180.
7. Kuiper GG, Lemmen JG, Carlsson B et al. *Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β*. Endocrinology 1998;139:4252-4263.
8. Müllner C, Sontag G. *HPLC with coulometric electrode array detection*. Eur Food Res Technol. 2000;211:301-304.
9. Durmaz E, Ozmert EN, Erkekoglu P et al. *Plasma phthalate levels in pubertal gynecomastia*. Pediatrics 2010;125:122-129.
10. Braun JM, Bellinger DC, Hauser R et al. *Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities*. Neurotoxicology, 2017;58:75-83.
11. Wang C-F, Tian Y. *Reproductive endocrine-disrupting effect of triclosan: Population exposure, present evidenceand potential mechamisms*. Environ Pollut. 2015;206:195-201.
12. Routledge EJ, Parker J, Odum J et al. *Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic*. Toxicol Appl Pharmacol. 1998;153:12-19.
13. Meeker JD. *Exposure to environmental endocrine disruptors and child development*. Arch Pediatr Adolesc Med. 2012;166:952-958.
14. Herbstman JB, Mall JK. *Developmental exposure to polybrominated diphenyl ethers and neurodevelopment*. Curr Environ Health Rep. 2014;1:101-112.
15. Roth N, Wilks MF. *Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: a systematic review of the epidemiological literature using a quality assessment scheme*. Toxicol Lett. 2014;230:271-281.
16. Dingemans MM, van den Berg M, Westerink RH. *Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system*. Environ Health Perspect. 2011;119:900-907.
17. Cowell WJ, Lederman SA, Sjödin A et al. *Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3-7 years*. Neurotoxicol Teratol. 2015;52:143-150.
18. Berg V, Nøst TH, Pettersen RD et al. *Persistent organic pollutants and the association with maternal and infant thyroid homeostasis: a multipollutant assessment*. Environ Health Perspectiv. 2017; 125:127-133.
19. Frederiksen M, Vorkamp K, Nielsen JB et al. *Polybrominated diphenyl ethers and novel flame retardants: associations between dust and human milk*. Conference abstract in: DUST2016, Castellaneta Marina, Italy, 12-17 June 2016, http://www.forskningsdatabasen.dk/en/catalog/2306906664
20. Hoffman K, Webster TF, Sjödin A et al. *Toddler's behavior and its impacts on exposure to polybrominated diphenyl ethers*. J ExposSci Environ Epidemiol. 2017;27:193-197.
21. Kortenkamp A. *Low dose mixture effects of endocrine disrupters: implications for risk assessment and epidemiology*. Int J Androl. 2008;31:233-240.
22. Fraser LR, Beyret E, Milligan SR et al. *Effects of estrogenic xenobiotics on human and mouse spermatozoa*. Hum Reprod. 2006;21:1184-1193.
23. Christiansen S, Scholze M, Axelstad M et al. *Combined exposure to anti-androgens causes markedly increased frequencies of hypospadias in the rat*. Int J Androl. 2008;31:241-248.
24. Ropero AB, Alonso-Magdalena P, Ripoll C, Fuentes E, Nadal A. *Rapid endocrine disruption: environmental estrogen actions triggered outside the nucleus*. J Steroid Biochem Mol Biol. 2006; 102:163-169.
25. Barker DJ. *The origins of the developmental origins theory*. J Inter Med. 2007;261:412-417.
26. Kavlock RJ, Ankley GT. *A perspective on the risk assessment process for endocrine-disruptive effects on wildlife and human health*. Risk Anal. 1996;16:731-739.

27. Ho SM, Cheong A, Adgent MA et al. *Environmental factors, epigenetics, and developmental origin of reproductive disorders*. Reprod Toxicol. 2017;68:85-104.
28. Swan SH. *Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans*. Environ Res. 2008;108:177-184.
29. Suzuki Y, Yoshinaga J, Mizumoto Y et al. *Foetal exposure to phthalate esters and anogenital distance in male newborns*. Int J Androl. 2012;35:236-244.
30. Main KM, Mortensen GK, Kaleva MM et al. *Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age*. Environ Health Perspect. 2006;114:270-276.
31. Gaspari L, Paris F, Jandel C et al. *Prenatal environmental risk factors for genital malformations in a population of 1442 French male newborns: a nested case-control study*. Hum Reprod. 2011; 26:3155-3162.
32. Cantonwine D, Meeker JD, Hu H et al. *Bisphenol a exposure in Mexico City and risk of prematurity: a pilot nested case control study*. Environ Health. 2010;9:62.
33. Adibi JJ, Hauser R, Williams PL et al. *Maternal urinary metabolites of Di-(2 Ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study*. Am J Epidemiol. 2009; 169:1015-1024.
34. Grandjean P, Gronlund C, Kjaer IM et al. *Reproductive hormone profile and pubertal development in 14yearold boys prenatally exposed to polychlorinated biphenyls*. Reprod Toxicol. 2012;34: 498-503.
35. Korrick SA, Lee MM, Williams PL et al. *Dioxin exposure and age of pubertal onset among Russian boys*. Environ Health Perspect. 2011;19:1339-1344.
36. Chen A, Chung E, DeFranco EA et al. *Serum PBDEs and age at menarche in adolescent girls: analysis of the National Health and Nutrition Examination Survey 2003–2004*. Environ Res. 2011; 111:831-837.
37. Den Hond E, Dhooge W, Bruckers L et al. *Internal exposure to pollutants and sexual maturation in Flemish adolescents*. J Expo Sci Environ Epidemiol. 2011;21:224-233.
38. Windham GC, Pinney SM, Voss RW et al. *Brominated flame retardants and other persistent organohalogenated compounds in relation to timing of puberty in a longitudinal study of girls*. Environ Health Perspectiv. 2015;123:1046-1052.
39. Lopez Espinosa MJ, Fletcher T, Armstrong B et al. *Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant*. Environ Sci Technol. 2011;45:8160-8166.
40. Zung A, Glaser T, Kerem Z et al. *Breast development in the first 2 years of life: an association with soy-based infant formulas*. J Pediatr Gastroenterol Nutr. 2008;46:191-195.
41. Wolff MS, Teitelbaum SL, Pinney SM et al. *Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls*. Environ Health Perspect. 2010;118:1039-1046.
42. D'Aloisio AA, Baird DD, DeRoo LA et al. *Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study*. Environ Health Perspect. 2010; 118:375-381.
43. de Cock M, de Boer M, Govarts E et al. *Thyroid-stimulating hormone levels in newborns and early life exposure to endocrine-disrupting chemicals: analysis of three European mother-child cohorts*. Pediatric Res. 2017;82:429-437.
44. Pop VJ, Kuijpens JL, van Baar AL et al. *Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy*. Clin Endocrinol. 1999;50:149-155.
45. Huang PC, Kuo PL, Guo YL et al. *Associations between urinary phthalate monoesters and thyroid hormones in pregnant women*. Human Reprod. 2007;22:2715-2722.
46. Botton J, Kadawathagedara M, de Lauzon-Guillain B. *Endocrine disrupting chemicals and growth of children*. Ann Endocrinol. 2017; 78:108-111.
47. Valvi D, Mendez MA,Garcia-Esteban R et al. *Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy*. Obesity 2014;22:488-496.
48. Vafeiadi M, Roumeliotaki T, Myridakis A et al. *Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood.* Environ Res. 2016;146:379-387.
49. Deierlein AL, Wolff MS, Pajak A et al. *Longitudinal associations of phthalate exposures during childhood and body size measurements in young girls*. Epidemiology 2016;27:492-499.
50. Kim BN, Cho SC, Kim Y et al. *Phthalates exposure and attention-deficit /hyperactivity disorder in school-age children*. Biol Psychiatry 2009;66:958-963.
51. Larsson M, Weiss B, Janson S et al. *Associations between indor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age*. Neurotoxicology 2009; 30:822-831.