Endocrine Disrupting Chemicals

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Endocrine-disrupting chemicals (EDCs) are exogenous substances able to mimic or to interfere with the endocrine system, thus altering key biological processes such as organ development, reproduction, immunity, metabolism and behavior. High concentrations of EDCs are found in several everyday products including plastic bottles and food containers and they could be easily absorbed by dietary intake. In recent years, considerable interest has been raised regarding the biological effects of EDCs, particularly Bisphenol A (BPA) and phthalates, on human pregnancy and fetal development. Several evidence obtained on in vitro and animal models as well as by epidemiologic and population studies strongly indicated that endocrine disruptors could negatively impact fetal and placental health by interfering with the embryonic developing epigenome, thus establishing disease paths into adulthood. Moreover, EDCs could cause and/or contribute to the onset of severe gestational conditions as Preeclampsia (PE), Fetal Growth Restriction (FGR) and gestational diabetes in pregnancy, as well as obesity, diabetes and cardiovascular complications in reproductive age. Therefore, despite contrasting data being present in the literature, endocrine disruptors must be considered as a therapeutic target. Future actions aimed at reducing or eliminating EDC exposure during the perinatal period are mandatory to guarantee pregnancy success and preserve fetal and adult health.

Endocrine-disrupting chemicals | Bisphenol A | Phthalates | Pregnancy | Reproductive Health | Obesity | Diabetes | Fetal Programming | Pregnancy-related disorders

1. Introduction

According to the World Health Organization (WHO), an endocrine disruptor is “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations”[1].

Endocrine Disrupting Chemicals (EDCs) disrupt endocrine functions mainly by mimicking natural hormones like estrogens, androgens or thyroid hormones. Moreover, they could alter hormones’ metabolism, thus blocking and antagonizing their interaction with the specific membrane and/or intra-cellular receptors[2]. Almost 800 chemicals are suspected to interfere with endocrine functions[3]. For example, dioxins are a byproduct in herbicide production, paper bleaching or in waste burning, while perchlorate is a secondary product of aerospace, weapon and pharmaceutical industries frequently found in drinking water[4][5]. Other EDCs are perfluoroalkyl and polyfluoroalkyl (PFAS), used in industrial applications as firefighting foams and non-stick pans[6]. Phytoestrogens are natural endocrine disruptors occurring in plants that have hormone-like activity, such as genistein and daidzein, that are in soy products like tofu or soy milk[7]. Of particular interest are BPA and phthalates, widely investigated as "obesogenic" factors that could interfere with pregnancy physiology and fetal development, thus being a leading cause of reproductive disorders[3]. Fresh meat, fish and vegetables which are not packed in plastic have a low concentration of BPA and phthalates[8], while ready-to-eat and fast food products stored in plastic bags and cans are a major exposure source to these EDCs[9][10].

BPA is an industrial chemical obtained from condensation between phenol and acetone that has been used to produce plastics and resins since the 1960s. It is considered the first synthetic estrogen produced, although it does not possess a steroid structure since it does not include the phenanthrene nucleus[11]. BPA is found in polycarbonate plastics that are commonly used in containers to store food, beverages and other goods. It is also present in epoxy resins used to coat metal products as food cans, bottle tops and water supply lines. Indeed, it is very easy to be exposed to BPA, and since 2011 the European Union prohibited BPA use at least in polycarbonate baby bottles. BPA was recently removed from many consumer products, being replaced by its structural analogs Bisphenol-S (BPS) and Bisphenol-F (BPF). Nevertheless, BPS and BPF have detrimental effects similar to BPA, such as cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like effects and neurotoxicity. Moreover, it has been shown that BPS and BPF exhibit estrogenic and/or anti-androgenic activities similar to or even greater than those of BPA[12][13]. While studies investigating BPS and BPF metabolism are lacking, BPA is absorbed by the digestive tract and, to a lesser extent, by the skin through direct contact[14]. After ingestion, BPA is metabolized by the intestinal microbiota and by the liver, mainly by glucuronidation and, to a lesser extent, sulfation, resulting in the production of BPA monoglucuronide (BPA-G) and BPA sulphate (BPA-S), with BPA-G being the main BPA metabolite in humans[15]. The majority of BPA is metabolized to BPA-G via the Uridine 5′-diphospho-glucuronosyltransferase (UGT) system. Studies on the fetal expression of UGT enzymes responsible for BPA glucuronidation detected no to low enzyme activity during the prenatal period[16]. Nevertheless, the human fetus is exposed to high BPA concentrations, since BPA-G and BPA-S are deconjugated and thus converted back to BPA in the placenta[17].

BPA is well known for its estrogenic activity exerted through the activation of the Estrogen Receptor (ER), with a stronger affinity for ERβ than for ERα, whereas BPA-G did not show ER-mediated estrogenic activity[18], but it exerted pro-inflammatory effects via the competitive inhibition of PPAR-γ signaling[19].

Phthalates are diesters of phthalic acid classified into high- and low-molecular-weight ones. The first category includes several compounds that are largely adopted to increase plastic flexibility and durability. Among them, the most commonly employed additive is di (2-ethylhexyl) phthalate (DEHP). Low-molecular-weight phthalates, like diethyl phthalate (DEP), are mainly used in personal care products and cosmetics, but they could be also found in pesticides and in food packaging[20]. Exposure to DEHP is reflected by the presence of its metabolites in urine, such as mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate, mono (2-ethyl-5-carboxypentyl) phthalate and mono(2-ethyl-5-oxohexyl) phthalate, whereas the main urinary metabolite of DEP is mono-ethyl phthalate (MEP). Remarkably, the bioactivity of phthalate metabolites is superior to that of the original substance[15].

2. Risk factors

BPA and phthalates are therefore widely present in everyday life due to the considerable volume of plastic produced[21]. They could be released at room temperature but heating facilitates their leaking out, resulting in massive food and beverage contamination[22]. For example, in polycarbonate (PC) bottles, high temperatures stimulate BPA migration into water by promoting hydrolysis and/or wall permeability[23], with a temperature that influences BPA migration more than heating time[24]. Table 1 summarizes the most important EDCs known to be disease risk factors.

Table 1. Endocrine-disrupting chemicals (EDCs) most relevant to human health.

EDC	Metabolites	Exposure Sources
Bisphenol[9] Bisphenol A (BPA) Bisphenol S (BPS) Bisphenol F (BPF) Bisphenol B (BPB)	[25] BPA glucuronide (BPA-G) BPA sulfate (BPA-S)	Synthetic[9] Food packaging; Thermal receipts; Plastic dinnerware; Polycarbonate plastic; Epoxy resins; Dental sealants;
High-Molecular-Weight Phathalate[9] Di(2-ethylhexyl) phthalate (DEHP)	[9] Mono(2-ethyl-5-hydroxyhexyl) phthalate; mEHHP Mono(2-ethylhexyl) phthalate; mEHP Mono(2-ethyl-5-oxohexyl) phthalate; mEOHP Mono(2-ethyl-5-carboxypentyl) phthalate; mECPP	Synthetic[9] Food packaging and processing; Pharmaceutical coatings; PVC plastics; Building materials; Medical devices;
Low-Molecular-Weight Phathalate[9] Diethyl phthalate (DEP)	[9] Monoethyl phthalate; mEP	Synthetic[9] Fragrant PCPs:| perfumes/colognes; deodorants; soaps,

		shampoos lotions;
Persistent Organic Pollutants (POPs) Dichlorodiphenyltrichloroethane (DDT)[26] Dioxins (PCDD, PCDF)[4]	chlorodiphenyldichloroethylene (DDE)	Synthetic Pesticides; [26] Insecticide; Combustion; [4] Incineration; Waste burning; Paper bleaching;
Polycyclic Aromatic Hydrocarbons (PAHs)[26] polybrominated diphenyl ethers (PBDEs) polychlorinated biphenyls (PCBs) brominated flame retardants (BFRs)		Synthetic[26] Combustion processes; Building materials; Electronics furniture; Hydraulic fluids;
Perfluorinated Alkylated Substances (PFAS)[6] Perfluoroalkyl Polyfluoroalkyl		Synthetic[6] Personal care products: Polishes and Paints; Non-stick cookware; Fire-fighting foams;
Phytoestrogens[7] Isoflavonoids (Genistein, Daidzein)		Natural[7] Soy beans and other legumes

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