



Review article

Human exposure to endocrine disrupting compounds: Their role in reproductive systems, metabolic syndrome and breast cancer. A review

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ABSTRACT

Endocrine disrupting chemicals (EDCs) are released into the environment from different sources. They are mainly used in packaging industries, pesticides and food constituents. Clinical evidence, experimental models, and epidemiological studies suggest that EDCs have major risks for humans by targeting different organs and systems in the body (e.g. reproductive system, breast tissue, adipose tissue, pancreas, etc.). Due to the ubiquity of human exposure to these compounds the aim of this review is to describe the most recent data on the effects induced by phthalates, bisphenol A and parabens in a critical window of exposure: *in utero*, during pregnancy, infants, and children. The interactions and mechanisms of toxicity of EDCs in relation to human general health problems, especially those broadening the term of endocrine disruption to 'metabolic disruption', should be deeply investigated. These include endocrine disturbances, with particular reference to reproductive problems and breast, testicular and ovarian cancers, and metabolic diseases such as obesity or diabetes.

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Abbreviation index and acronym: 11-HSDs, 11-hydroxysteroid dehydrogenases; 3-HSD, 3-hydroxysteroid dehydrogenase; 5-Cx-MEHP, Mono-(2-ethyl-5-carboxypentyl) 1,2-benzenedicarboxylate; 6-OH-MEHP, Mono-(2-ethyl-6-hydroxyhexyl) 1,2-benzenedicarboxylate; AR, Androgen receptors; BBP, Benzyl butyl phthalate; BC, Breast Cancer; BMI, Body mass index; BP, Blood pressure; BPA, Bisphenol A; ButP, Butyl paraben; bw, body weight; DBP, Dibutyl phthalate; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloroethane; DEHP, Di-(2-ethylhexyl) phthalate; DEP, Di-ethyl phthalate; DIBP, Di-isobutyl phthalate; DMP, Di-methyl phthalate; dw, dry weight; E2, 17-β-estradiol; EC, European Commission; EDI, Estimated Daily Intake; EDCs, Endocrine disrupting chemicals; EFSA, European Food Safety Authority; ERR_γ, Estrogen-related receptor gamma; ER, Estrogen receptor; ER_α, Estrogen receptor α; ER_β, Estrogen receptor β; EthP, Ethylparaben; FAI, Free androgen index; fw, fat weight; GR, Glucocorticoid receptors; GnRH, Gonadotropin-releasing hormone; HMW, High molecular weight; IL-6, Interleukin-6; iso-ButP, iso-butylparaben; LH, Luteinizing hormone; LMW, Low molecular weight; MBP, Monobutylphthalate; MBzP, Mono-benzyl phthalate; MCF-10A, Human breast epithelial cells; MCNP, Mono-(carboxylnonyl) phthalate; MCOP, Mono-(carboxyoctyl) phthalate; MECPP, Mono-2-ethyl-5-carboxypentyl phthalate; MEHHP, Mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, Mono(2-ethylhexyl) phthalate; MEOHP, Mono-(2-ethyl-5-oxohexyl) phthalate; MEP, Monoethyl phthalate; MetP, Methylparaben; MiBP, Mono-isobutyl phthalate; MMP, Monomethyl phthalate; MOFs, Multiple oocyte follicles; MR, Mineralocorticoid receptors; NHANES, National Health and Nutrition Examination Survey; n-ButP, n-butylparaben; n-PropP, n-propylparaben; PAEs, Phthalate esters; PB, Parabens; PBDEs, Polybrominated diphenyl ethers; PCOS, Polycystic ovarian syndrome; PCPs, Personal care products; PD, Parkinson's disease; PHBA, P-hydroxybenzoic acid; PHTs, Phthalates; POPs, Persistent organic pollutants; PPAR, Peroxisome proliferator-activated receptors; PR, Progesterone receptor; PropP, Propylparaben; PVC, Polyvinyl chloride; T2DM, Type 2 diabetes mellitus; TDI, Tolerable Daily Intake; TDS, Testicular dysgenesis syndrome; TR, Thyroid receptors; ww, wet weight

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1. Introduction

According to the definition adopted by the European Union “an endocrine disruptor is an exogenous substance or mixture that alters the function of the endocrine system, causing adverse effects on the health of an organism, or its progeny, or (sub)population” (European Workshop on the Impact of Endocrine Disruptors on Human Health and Wildlife, Weybridge, UK, 2–4/12/1996).

Endocrine disrupting chemicals (EDCs) are pseudo-persistent compounds present in the environment at very low levels; however, these low concentrations are sufficient to cause adverse effects leading to a variety of health problems, such as reproductive damage, developmental impairment, and cancer in females and males (Abaci et al., 2009; Nohynek et al., 2013). Additionally, EDCs contribute to the progression of some metabolic disorders including obesity, diabetes, and endometriosis (Diamanti-Kandarakis et al., 2009; Legler et al., 2015).

Exposure to EDCs starts in utero and never ceases throughout life since these chemicals are present in a large variety of daily products like: food, flame retardants, plastic bottles, metal food cans, detergents, toys, sun lotion, cosmetics, and pesticides (Colborn et al., 1993; Harvey and Darbre, 2004; Guo et al., 2014; Juhász et al., 2014; Maipas and Nicolopoulou-Stamati, 2015).

The identification and safety assessment of potential EDCs is complicated by the observed low-dose effects and non-monotonic dose responses (Vandenberg et al., 2012) as well as the often long-term exposure or exposure during a critical window early in development (Hond and Schoeters, 2006).

EDCs can interfere with endocrine functions, either by directly activating or inactivating endocrine target receptors or by disrupting the synthesis of hormones or the local control of active to inactive hormones by inhibiting or activating their metabolizing enzymes.

The classical EDC targets are nuclear receptors such as estrogen receptors (ER), androgen receptors (AR), mineralocorticoid receptors (MR), progesterone receptors (PR), glucocorticoid receptors (GR), thyroid receptors (TR) and peroxisome proliferator-activated receptors (PPAR) (Yang et al., 2015; Wuttke et al., 2010).

Furthermore, studies demonstrate the ability of these compounds to act on hormone metabolizing enzymes, including aromatase (Sanderson, 2006), 5-reductase (Kalfa et al., 2009), 3-hydroxysteroid dehydrogenase (3-HSD) (Ye et al., 2011) and 11-

hydroxysteroid dehydrogenases (11- HSDs) (Odermatt et al., 2006; Guo et al., 2012), and to impact on nuclear receptor responses by altering the availability of active hormones.

Endocrine disruption affects various body functions, depending on the pathway that is disrupted. EDCs are capable of altering the normal action carried out by estrogens and androgens, inhibiting synthesis or interfering with the metabolism of sex steroids (Lee et al., 2013a). EDCs with adverse effects on reproduction bind either to the estrogen receptors (ERs) or to the androgen receptor (AR) and, by doing so, may either stimulate or inhibit the transcriptional or post-transcriptional mechanisms (Wuttke et al., 2010).

Synthetic EDCs are broadly categorized into short-lived pollutants that are ubiquitous in the environment and persistent organic pollutants (POPs). Short-lived pollutants include phthalates (PHTs) and bisphenol A (BPA), found ubiquitously in plastics. POPs include the organochlorine pesticides dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE), industrial byproducts, such as dioxins, and flame retardants, such as polybrominated diphenyl ethers (PBDEs). The goal of this article is to review the environmental sources of EDCs, specifically phthalates, bisphenol A and parabens, and their adverse effects on human health, with special focus on the reproductive system, obesity, and diabetes, and paying especial attention to critical windows of exposure (fetuses, infants and children) (Calafat et al., 2010; Wolff et al., 2008; Woodruff et al., 2011). Focus on these special aspects is considered relevant and timely in the current context, given the documented changes in the onset of puberty worldwide in the last decade (Özen and Darcan, 2011), the epidemic numbers of obesity (Heindel et al., 2015), and the increased incidence of diabetes (Chevalier and Fénelichel, 2015), especially in developed countries.

2. EDC categories of interest

2.1. Phthalates

Phthalate esters (PAEs) are a class of widely distributed industrial chemicals, used as plasticizers mainly to soften polyvinyl chloride-based (PVC) products. Many consumer products contain specific members of this family of chemicals, including building materials, household furnishings, clothing, medical devices,

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