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Estrogenic and anti-androgenic endocrine disrupting chemicals and their impact on the male reproductive system

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Endocrine disrupting chemicals (EDCs) are identified for their ability to perturb the homeostasis of endocrine system and hormonal balance. The male reproductive system is under close control of hormones and each change in their concentration and time of exposition and action can induce a deregulation of its physiology. In this review we summarize the most recent studies on two main categories of EDCs with different action: the estrogenic bisphenol A and alkylphenols and the anti-androgenic phthalates. This review describes the main effects of these substances on male reproductive system.

Keywords: endocrine disrupting chemicals (EDCs), bisphenol A (BPA), nonylphenol (NP), phthalates, Testicular Dysgenesis Syndrome (TDS)

INTRODUCTION

Environmental compounds belonging to endocrine disrupting chemicals (EDCs) are an heterogeneous group of ubiquitous synthetic or natural substances defined according to three criteria: endocrine activity, adversity of effects and a possible correlation cause-effect (Alexander et al., 2013; Svechnikov et al., 2014). EDCs can be used in industry for many different applications such as lubricants and solvents (polychlorinated biphenyls [PCB], polybrominated diphenyl ethers [PBDE] and dioxins) (Shi et al., 2007; Darnerud, 2008; Pocar et al., 2012), plastics (bisphenol A [BPA], and bisphenol S [BPS]) (Rubin, 2011; Vinas and Watson, 2013), plasticisers (phthalates) (Hauser and Calafat, 2005), pesticides and herbicides (atrazine, cypermethrin, dichlorodiphenyltrichloroehane [DDT], dieldrin, methoxychlor [MXC], and vinclozolin [VCZ]) (Kavlock and Cummings, 2005; Tiemann, 2008; Hayes et al., 2011; Wang et al., 2011), and organic compounds (diethylstilbestrol [DES], ethyl estradiol [EE]) (Herbst et al., 1971; Hogan et al., 2010). It has been shown that the primary source of human and animal exposure is the diet since the population is exposed to EDCs mainly through ingestion of contaminated food or water. However, a further exposure can also happen through inhalation of contaminated air and dust or through skin contact (Jeng, 2014). Moreover, recently it has been shown that human exposition can occur through medical consumables and devices such as catheters, breathing and respiratory equipment and blood bags containing different mixtures of EDCs (Ponzo and Carbone, 2013). EDCs can affect multiple endocrine pathways, hormonal and homeostatic systems, but they particularly influence and perturb the steroidogenesis and the reproduction since most of the effects are exerted through disturbance of estrogen or androgen-mediated processes (del Mazo et al., 2013; Knez, 2013; Marques-Pinto and Carvalho, 2013; Zhang et al., 2014). Many EDCs are xeno-estrogens able to bind the estrogen receptor (ER) with an affinity 1000-fold lower than that of estrogen (Lee et al., 2013). Specifically, EDCs can affect cells and biological systems through different mechanisms, by agonistic or antagonistic interaction with hormone receptors, altering the production of endogenous hormones (the synthesis, transport, and metabolism) and even inducing intersex (Lange et al., 2009; Zhao and Hu, 2012; Cao et al., 2013; Ji et al., 2013; Svechnikov et al., 2014; Yu et al., 2014). Other less well known mechanisms of action of EDCs include alterations of genetic systems (Edwards and Myers, 2007; del Mazo et al., 2013), direct effects on genes (Moral et al., 2008) and the EDC epigenetic impact (Anway and Skinner, 2008). These effects are particularly troubling since alterations in genetic programming during early stages of development may have profound effects years later and may also lead to transgenerational inheritance of disease (Schug et al., 2011; Skinner, 2011). Environmental substances are considered accountable for the increasing incidence of human reproductive diseases and the consequent decline in reproductive function worldwide (Balabanic et al., 2011; Woodruff, 2011; Marques-Pinto and Carvalho, 2013). It has been demonstrated that over 50 years, the global average sperm count dropped by half, from 113 to 66 million/ml (about 1% at year), whereas sperm morphology/motility abnormalities significantly increased (Carlsen et al., 1992; Marques-Pinto and Carvalho, 2013). The reproductive male function in humans is regulated by a number of hormones and paracrine factors (Svechnikov et al., 2014). Hence, in order to study disturbances, it is important to consider

first the physiological mechanisms of a healthy sperm production (Knez, 2013). The development of the male reproductive system requires the activation of specific pathway by hormones, such as androgens and anti-Müllerian hormone (AMH). Testis cell development is dependent on the local action of hormones, such how most aspects of masculinization depend on normal testicular hormone production (Knez, 2013). Normal testicular development in fetus depends on the differentiation and development of Leydig and Sertoli cells, which are necessary for the subsequent development of reproductive tract (Magre and Jost, 1991; Lejeune et al., 1998; Yu et al., 2014). Fetal Leydig cells (FLCs) are a major source of androgens in the prenatally developing male (Svechnikov et al., 2014). The Sertoli cells, considered as nurse cells for spermatogenesis, are the first cells that can be identified in the early fetal testis and are crucial for the seminiferous cord formation and Leydig cell functionality (Sharpe et al., 2003; Svechnikov et al., 2014). Moreover, the Sertoli cells secrete AMH, which induces the regression of the Müllerian duct (Wilson, 1978; Svechnikov et al., 2014). Specific gene expression together with autocrine, paracrine and endocrine regulations allow the continuous production of sperm in adult life (Brennan and Capel, 2004; Park and Jameson, 2005; del Mazo et al., 2013). The rapid increase in reproductive disorders suggests that environmental or lifestyle factors, rather than genetic defects are the most likely causes (Svechnikov et al., 2014). Specifically, previous researches on male reproduction have mainly focused on changes at the level of serum testosterone (Zhang et al., 2014). This androgen, together with dihydrotestosterone (DHT) that is produced locally from testosterone by 5-α-reductase, play a pivotal role in the masculinization of external genitalia and prostate of the male fetus, driving the process of "making a male" during a specific period of fetal development named "masculinization programming window" (Fisher, 2004; Welsh et al., 2008; Scott et al., 2009; Knez, 2013; Svechnikov et al., 2014). In humans this window extends from 6.5 to 14 gestational week (N'Tumba-Byn et al., 2012); whereas, testosterone reaches its maximal values between 11 and 18 weeks of gestation and stimulates differentiation of the Wolffian duct into epididymis, vas deferens and seminal vesicles and prostate (Svechnikov et al., 2014). On the contrary, differentiation of prostate and external genitalia (penis, scrotum, and perineum) is mediated by DHT (Svechnikov et al., 2014). It seems likely that the abnormal development of testes in fetal and neonatal life can have long-term consequences for sperm production (Sharpe, 2001; Knez, 2013). Although androgens are the most important hormones in the normal development of the male reproductive system (Knez, 2013), more recently, it has been suggested a central role for estrogen in testicular function, due to the presence of large quantities of estrogen in the rete testis fluid and spermatic veins of numerous mammals (Hess, 2003; Zhang et al., 2014). So, the balance between androgens and estrogens may be important in maintaining normal spermatogenesis (Zhang et al., 2010, 2014; Williams et al., 2011). Therefore, the exposition to xenoestrogens and anti-androgens during fetal and neonatal development has been associated with a series of male reproductive disturbances, such as cryptorchidism, hypospadias, impaired fertility (especially due to poor semen quality), and an elevated incidence of testicular cancer (McLachlan et al., 1975; Gill et al., 1979; Jensen et al., 1995; Zhang et al., 2014). These four clinical and etiologically related symptoms have been assembled in the Testicular Dysgenesis Syndrome (TDS) (del Mazo et al., 2013) and they probably arise from intrauterine disruption of proper testicular development and function (Vega et al., 2012) under EDCs exposure (Massart and Saggese, 2009; Marques-Pinto and Carvalho, 2013). Thus, TDS entries in the concept of DOHaD (Developmental Origins of Health and Disease) (Schug et al., 2011). The perinatal period is one of the sensitive windows of development wherein minor hormonal perturbations may have a long lasting impact on fertility (Saunders et al., 1997; Si et al., 2015). So, endocrine disruption in developing organism may determine the propensity of individual to develop a disease or dysfunction later in life (Barker, 2004; Diamanti-Kandarakis et al., 2009). In fact, it is well accepted that a lag between the time of exposure to EDCs and the manifestation of a disorder can occur (Diamanti-Kandarakis et al., 2009; Isling et al., 2014). Furthermore, many EDCs influence the anogenital distance, a parameter used as biomarker of reproductive effects.

Many studies based on epidemiological data show links between environmental factors and hypospadias and cryptorchidism. Hypospadias is a condition that affects about 0.4% of males in which the opening of the urethra is on the ventral side of the penis rather than at the tip of the glans penis (Marques-Pinto and Carvalho, 2013; Jeng, 2014). Hypospadias may arise during the first trimester of *in utero* life and it is classified as mild (first degree) to severe (third degree) (Jeng, 2014). Specifically, it has been demonstrated that exposure of male fetuses *in utero* to different EDCs such as vinclozolin, PCBs, phthalates and dioxins (Kristensen et al., 1997; Baskin et al., 2001; Gray et al., 2001; Fisher et al., 2003) or residence location in the vicinity of hazardous waste disposal sites induce hypospadias in boys of the resident families (Dolk et al., 1998; Elliott et al., 2001; Svechnikov et al., 2014). An example is Seveso industrial accident that induced a high incidence of hypospadias in male children of parents exposed to dioxin (Mastroiacovo et al., 1988). Father or mother (Vrijiheid et al., 2003) occupational exposures such as farmer handling herbicides (Garry et al., 2002), firemen (Schnitzer et al., 1995) or vehicle mechanics (Irgens et al., 2000) has been shown to highly contribute to incidence of this malformation (Svechnikov et al., 2014). Although cryptorchidism is often considered a mild malformation, it represent the best characterized risk factor for infertility and testicular cancer in adulthood (Svechnikov et al., 2014). It is defined as the failure of one or both testicles to descend into the scrotal sac which likely occurs by 6 months of age and it is the common congenital abnormality in male children, affecting 2–4% of full-term males (Boisen et al., 2004; Marques-Pinto and Carvalho, 2013). Multiple studies suggest the interaction between EDCs in etiology of this disorder. Specifically, EDCs with antiandrogenic (Stoker et al., 2005) or estrogenic effects such as organohalogen pollutants, phthalates and compounds like PBDEs (Main et al., 2007) or DES (Stillman, 1982) have the potential of disturbing cellular events that control the testicular descent in humans (Svechnikov et al., 2014). Moreover, EDCs such as dibromochloropropane, ethylene dibromide, chlordecone, organophosphate may directly affect spermatogenesis by damaging the spermatogonia, destroying Sertoli

cells or changing the morphology or motility of spermatozoa (Sever et al., 1997; Padungtod et al., 2000; Bretveld et al., 2007; Svechnikov et al., 2014). The late detrimental effects are semen quality, sperm count, motility and morphology (Svechnikov et al., 2014).

This review describes the effects of two main categories of EDCs: bisphenol and alkylphenols and phthalates that show opposite actions (xenoestreogens and anti-androgens) on the male reproductive system.

BPA AND ALKYPHENOLS

BISPENOL A

BPA (4,4-dihydroxy-2,2-diphenylpropane) is a xenoestrogenic endocrine-disrupting chemical used in the manufacture of polycarbonate plastics and epoxy resins, such as food and drink containers, plastic water bottles, baby bottles, dental sealants and a variety of household products (compact disks, consumer electronics) (Knez, 2013; Liu et al., 2013). It is widespread in the environment and every year 2.2–4.7 million tons of BPA are released into the environment, of which around 1.2 million tons are produced in EU and the amounts are rising by about 6–8% yearly (Fernandez, 2010; Vandenberg et al., 2010; Huang et al., 2012; Knez, 2013; Liu et al., 2013). Human beings are mainly exposed to BPA via dietary ingestion of leachings from the inner lining of cans and microwave containers during heating of food materials of through beverages in polycarbonate bottles due to repeated usage or contact with acid/alkaline (Biles et al., 1997; Jeng, 2014). It has been valued that the human body is exposed to concentrations of 10 μg/day of BPA and it can be detected in several human body samples, such as serum, urine, amniotic fluid of pregnant women, breast milk and even in semen (Inoue et al., 2002; Calafat et al., 2005; Carlsen et al., 2005; EC-SCF, 2006; Phillips and Tanphaichitr, 2008; Lagos-Cabré and Moreno, 2012). BPA quantification in amniotic fluid and in umbilical cord reported a mean level around 1 ng/ml (Fenichel et al., 2012; N'Tumba-Byn et al., 2012). It has been estimated that urinary BPA is detected in >90% of Americans (Lang et al., 2008; Liu et al., 2013). Furthermore, it has been proposed that BPA might accumulate particularly in early fetuses because of lower metabolic clearance of conjugation at this development stage (Ikezuki et al., 2002; N'Tumba-Byn et al., 2012). Several studies have shown that increased urine BPA levels may be associated with decreased sperm concentrations (Li et al., 2011), decreased semen quality and increased single strands breaks of sperm DNA damage (Meeker et al., 2010; Liu et al., 2013). Moreover, it has been demonstrated that in males, BPA and estrogen perinatal exposure affects fertility and has the potential to induce blood-testis barrier restructuring (Li et al., 2009), disruptions in Sertoli cell junctional proteins (Salian et al., 2009), germ cell apoptosis, and disruption of spermatogenesis (Liu et al., 2013). All these targets by BPA and estrogens highlight ability of these compounds to perturb normal cell morphology and homeostasis inducing cell deregulation. All these cell alterations may lead to infertility in adulthood through germ loss via immunological activity (Toyama and Yuasa, 2004; Salian et al., 2009; Marques-Pinto and Carvalho, 2013). Recent findings suggest that human fetal steroidogenesis is highly sensitive to low environmentally relevant doses of BPA through the involvement of ER receptor and/or membrane-bound GPR30 in the regulation of the hormonal function of human FLCs (N'Tumba-Byn et al., 2012; Svechnikov et al., 2014). In humans, it has been demonstrated a positive correlation between BPA and total/free testosterone values in men and that BPA is related to lower FSH concentrations (Hanaoka et al., 2002; Knez, 2013). Moreover, a significant inverse association has been detected among urinary BPA concentrations free androgen index (FAI) levels and the FAI/LH ratio, as well as a positive association between BPA and sex hormone-binding globulin (SHBG) suggesting that BPA concentrations may be linked to subtle variations in sex hormones in fertile men (Lagos-Cabré and Moreno, 2012). Great attention should be done to animal model used in toxicological and endocrinological studies of EDC effects, since marked differences can be recorded. For example, as indicated by Richter et al. (2007) the outbred Sprague-Dawley CD rat from Charles River Laboratories has very low sensitivity to exogenous estrogens in contrast to male and female CD-1 (ICR) mice that are highly sensitive to EDC exposure (Richter et al., 2007). It has been demonstrated that prenatal, perinatal and adult exposure to BPA causes developmental genitourinary anomalies, decreased epididymal weight, daily sperm production or increased prostate weight in laboratory rodents. Several studies have confirmed that BPA is able to induce detrimental effect at doses lower than 50 mg/kg/day, which is currently accepted in USA as the lowest dose used to estimate the lowest observed adverse effect level (LOAEL) and so to calculate the acceptable daily intake in humans (Nagel et al., 1997; vom Saal et al., 1998; Williams et al., 2001; Richter et al., 2007; Salian et al., 2009; Knez, 2013). The dangerousness of EDCs and also of BPA is that these substances are able to induce different and multiple effects on several target cells and organs also in a non-linear manner and at not predictive concentrations. So, researches on EDCs would necessarily use appropriate positive and negative controls. For example, in a study performed on male mice with 40 μg/kg for 7 weeks, it has been observed a marked decrease in the number of spermatozoa, semen quality and abnormal spermatogenesis (Lee et al., 2013). In neonatal male rats treated for 5 days with BPA was observed a low sperm count and motility in adulthood, accompanied by a low mating rate and sloughing of germ cells, demonstrating a long-term effects of this substance (Salian et al., 2009; Lagos-Cabré and Moreno, 2012). A reduction on Leydig cell numbers, multinucleated germ cells (MNGs) and T plasma levels have been observed in pubertal mice orally receiving 160–960 mg/kg of BPA for 13 days (Takao et al., 2003; Li et al., 2009; Lagos-Cabré and Moreno, 2012). These results highlight the BPA negative power to influence and perturb male reproductive system in different stages. It has been demonstrated that exposure to environmentally relevant BPA levels has adverse effects on testicular function by decreasing pituitary LH secretion and reducing Leydig cell steroidogenesis (Akingbemi et al., 2004; Svechnikov et al., 2010). Through *in vitro* studies, it has been shown that BPA act directly in Leydig cells decreasing testosterone production (Akingbemi et al., 2004; Svechnikov et al., 2010). An other target inside the male reproductive system is the prostate which development and differentiation as well as the maintenance of adult homeostasis is regulated by both androgens and estrogens (Arase et al., 2011). Fetal exposure to low-dose BPA (10 μg/kg/day)

increased cell proliferation of urogenital sinus epithelium (UGE) in the primary prostatic ducts of CD1 mice (Timms et al., 2005; Arase et al., 2011). This effect was confirmed also by *in vivo* study where low-dose BPA (20 μg/kg/day) increased the number of basal epithelial cells in the adult prostate of BALB7c mice and induced permanent cytokeratin 10 expression in such cells similar to the effects of DES (Ogura et al., 2007; Arase et al., 2011). Several studies have shown that prenatal exposure to BPA causes hyperplasia of prostate in male rats resulting in greater risk of prostate cancer (Ho et al., 2006; Jeng, 2014). Moreover, neonatal exposure of male rats to low-dose BPA (10 μg/kg/day) elicited critical molecular changes during prostate development and also increased prostatic gland susceptibility to precancerous neoplastic lesions and hormonal carcinogenesis (Ho et al., 2006; Arase et al., 2011). Furthermore, it has been demonstrated that also in the prostate such as in other reproductive organs BPA was able to negatively affect the *in situ* steroidogenesis inducing an increase of aromatase activity (Arase et al., 2011).

ALKYLPHENOLS

Alkylphenols are used as industrial intermediaries and surfactants in the production of non-ionic detergents, latex paint, adhesives and plastics as the polystyrene, polymer stabilizers to package food, common consumer products such as detergents, disinfectants, surface cleaners, cosmetic products, herbicides and pesticides, and also antioxidant agents and lubricant additives (Soto et al., 1991; Inoue et al., 2001; Shaw and McCully, 2002). The annual production of alkylphenols has been estimated to be 154,000 tons in the USA and 75,000 tons in the EU (Soares et al., 2008; Knez, 2013). The most important members of this group are nonylphenol ethoxylate (NPE) and octylphenol ethoxilate (OPE) (Tubau et al., 2010; Knez, 2013). These substances undergo metabolic breakdown in the environment and lose ethylene oxide side chains to become alkylphenols (4-n-octylphenol and 4-n-nonylphenol). Unlike most of the exogenous chemicals, which usually become less toxic with biodegradation, alkylphenols actually increase their toxicity during this process (Knez, 2013). The main exposition source for humans is the food and all these substances or their metabolites have been detected in human urine, serum, amniotic fluid of pregnant women, in breast milk and even in semen (Guenther et al., 2002; Calafat et al., 2005; Main et al., 2006; Huang et al., 2009; Knez, 2013). It has been valued that the human body is daily exposed to about 7.5 μg/day of nonylphenol (NP) (Lagos-Cabré and Moreno, 2012). In rodent models exposed to NP or OP, it has been shown a testicular damage with a decrease in the testicular size and weight, in the epididymis and sperm production, an increase of the intertubular space and low seminal quality (Jager et al., 1999; Lee et al., 1999; Chitra et al., 2002; Herath et al., 2004; Lagos-Cabré and Moreno, 2012; Knez, 2013; Ponzo and Carbone, 2013). Moreover, NP exposure neonatally, in early stages of sexual maturation and in adulthood rat, led to a histological disorganization of the epithelium seminiferus of testis (Ponzo and Carbone, 2013), a reduction in testis, epididymis and seminal vesicle size other than an increase of cryptorchidism up to a 60% (Lee, 1998; Nagao et al., 2001; Fan et al., 2010; Ponzo and Carbone, 2013). All these results clearly demonstrate that alkylphenols and particularly NP are able to influence the correct development and physiology of male reproductive system, specifically target testis and epididymis. These organs are particularly important for the quality of spermatozoa and reproductive fitness. Moreover, NP administration to pregnant rats during gestation, lactancy and 10 weeks after weaning (corresponding to a complete lifespan exposed to NP) have been shown to decrease epithelial thickness, probably due to Sertoli cells shrinking and an increase in germ cell apoptosis (De Jager et al., 1999; McClusky et al., 2007; Lagos-Cabré and Moreno, 2012). Moreover, NP administered to rats during adulthood and also from fetal development until adulthood decreased testosterone levels (Laurenzana et al., 2002; Gong and Han, 2006; Ponzo and Carbone, 2013). So, NP is able to have various cell targets and to activate and deregulate different cell pathways involved in testis physiology and testosterone production.

PHTHALATES

Phthalates are industrial chemicals with very different applications and toxicological properties. Specifically, they are used as plasticizers to add softness, flexibility, durability, transparency, and longevity to a variety of consumer, industrial, and medical products (Johnson et al., 2012; Martinez-Arguelles et al., 2013). They are broadly used in the manufacture of plastics, solvents, sealants, paints, varnishes, detergents, cosmetics, and personal care products, toys, household products, as well as in the food processing, medical and pharmaceutical industries (Jurewicz and Hanke, 2011; Wittassek et al., 2011; Johnson et al., 2012; Moody et al., 2013). They are classified in two distinct groups based on molecular weight: (a) high molecular weight compound (di-2-ethylexyl phthalate–DEHP), primarily used as plasticizers in the manufacture of flexible vinyl plastic present in consumer products, flooring and wall covering and medical devices [Agency for Toxic Substances and Disease Registry (ATSDR), 2002; Jeng, 2014]; (b) low molecular weight compounds (diethyl phthalate, dibutyl phthalate, DBP), used in personal care products such as solvents for perfumes and fixatives for hair spray (Chen et al., 2011), as solvents and plasticizers for cellulose acetate (Jeng, 2014). Thus, they can be found in food containers, adhesives, perfumes and eye shadow (Knez, 2013). Moreover, many importance have been done to phthalate metabolites such as three di-(2-ethylexyl) phthalates, mono-(2-ethylexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) (Jeng, 2014). Among phthalates, DEHP is the most widely used to convey flexibility and transparency to numerous plastics made of polyvinyl choride (PVC) (Latini et al., 2003; Ponzo and Carbone, 2013). Since phthalates are not covalently bound to the polymer, they can leach from plastics into foods, beverages and body fluids (Lovekamp and Davis, 2001; Moore et al., 2001; Ponzo and Carbone, 2013) with product age, use, and ultraviolet light exposure, making them available for biological exposure (Thomas and Thomas, 1984; Johnson et al., 2012). In fact, human exposure occurs by ingestion, absorption, inhalation and dermal exposure, and different studies confirmed phthalate metabolite presence in human urine, breast milk samples and some serum (Hines et al., 2009; Frederiksen et al., 2011; Göen et al., 2011; Wittassek et al., 2011; Moody et al., 2013). In humans,

maternal exposure to phthalates (Adibi et al., 2003, 2009; Latini et al., 2003; Swan et al., 2005; Martinez-Arguelles et al., 2013) provides the first source of fetal exposure, through amniotic fluid (Silva et al., 2004), umbilical cord blood (Latini et al., 2006), and other bodily fluids (Silva et al., 2005; Martinez-Arguelles et al., 2013). It is reckoned that around 6 million tons of phthalates are produced worldwide every year (Rudel and Perovich, 2009; Knez, 2013). Typical daily phthalate intake in humans is estimated at 1.7–52.1 μg/kg/day (Doull et al., 1999; Koch et al., 2003; McKee et al., 2004; Frederiksen et al., 2011; Martinez-Arguelles et al., 2013), whereas children exposure is 2- to 4-fold higher than adults (Koch et al., 2005; Moody et al., 2013). Moreover, individuals, especially children with long-term medical conditions have much greater exposure than general population since the use of phthalates in medications and medical devices (Moody et al., 2013), with an estimated exposure of 20 mg phthalate per day (Plonait et al., 1993; Green et al., 2005; Su et al., 2012; Moody et al., 2013). Phthalates are considered to be one of the major groups of anti-androgenic substances (Grady and Sathyanarayana, 2012; Knez, 2013). Several toxicological studies have demonstrated a link between phthalate exposure and disorders of male reproductive development, such as hypospadias, cryptorchidism, smaller testes and penis size, alterations of the vas deferens and epididymis, reduction of the anogenital distance and the presence of MNGs (Cortes et al., 2003; Fisher et al., 2003; Foster, 2006; Knez, 2013), and adult pathologies such as Leydig cell aggregation (Hoei-Hansen et al., 2003; Holm et al., 2003; Nistal et al., 2006), Sertoli cell-only tubules, poor spermatogenesis (Nistal et al., 2006), testicular germ cell tumors and reduced semen quality (Moody et al., 2013; Jeng, 2014). Moreover, in two independent studies, phthalate levels in urine from pregnant women have shown significant inverse correlations with AGD of their male offspring (Swan et al., 2005; Suzuki et al., 2011; Johnson et al., 2012). Furthermore, exploring the neonatal maternofetal unit, it has been observed an inverse correlation between phthalate levels in human breast milk and serum-free testosterone in their suckling males and a positive correlation between breast milk phthalate levels and serum luteinizing hormone/testosterone ratios (Main et al., 2006; Johnson et al., 2012). Recently, a study conducted on 463 men found significant dose-response associations between mono-butyl phthalate (MBP) concentration and low sperm concentration and low motility (Hauser et al., 2006; Jeng, 2014). An other study on 344 men who had normal semen concentration have shown that several urinary phthalate metabolites (5-OH-MEHP, MEHP, mono-isobutyl phthalate MiBP) were significantly associated with a decrease in sperm motility (Jurewicz et al., 2013; Jeng, 2014). By the use of human man models, it is possible speculate that in our species phthalates are able to influence hormonal homeostasis and balance in male reproductive system inducing a deregulation of normal sperm activity. Moreover, using animal models, it has been shown that DEHP results in testicular toxicity and impaired steroidogenesis and can cause birth defects (Srivastava et al., 1990; Park et al., 2002; Ponzo and Carbone, 2013; Jeng, 2014) producing a phenotype termed the "phthalate syndrome" that comprises non-descent of testis, malformations of external genitalia, poor semen quality, and malformations of other sex organs (Foster, 2006; Johnson et al., 2012). It has been demonstrated that exists a critical *in utero* exposure window for reproductive malformations. The critical phthalate exposure window for reproductive tract lesion development encompasses approximately GD16-GD18 (Ema et al., 2000; Carruthers and Foster, 2005; Johnson et al., 2012). However, phthalates inhibit fetal testis testosterone production during the entire fetal period when the testis is highly steroidogenic (Parks et al., 2000; Thompson et al., 2004, 2005; Plummer et al., 2007; Scott et al., 2008; Hannas et al., 2011; Johnson et al., 2012). *In utero* phthalate exposure alters seminiferous cord development with delayed maturation, focal, dysgenetic cords with intracordal Leydig cells and, more generally, cords with larger diameters harboring a large number of MNGs (Boekelheide et al., 2009; Johnson et al., 2012). The primary target cells of phthalate exposure seem to be mesenchymal and peritubular myoid cells which functional changes lead to functional perturbations of Leydig, Sertoli, and germ cells (Johnson et al., 2012). Sertoli cells are the next apparent target for phthalate-induced effects on the seminiferous cords, manifesting immaturity and alterations in their apical processes, cytoskeleton, and interactions with germ cells (Fisher et al., 2003; Kleymenova et al., 2005; Johnson et al., 2012). Phthalate exposure reduces the percentage of proliferating rat Sertoli cells by about 40% (Hutchison et al., 2008; Scott et al., 2008; Johnson et al., 2012). Because Sertoli cell proliferation depend on Leydig cell testosterone output (Scott et al., 2007), the decrease of Sertoli cell proliferation is downstream of Leydig cell steroidogenic inhibition (Johnson et al., 2012). For these reason the critical phthalate exposure window for Sertoli cell proliferation effects is between GD19 and GD21 (Scott et al., 2008; Johnson et al., 2012). These results performed on animal models highlight some of possible cell targets of phthalates that in turn can explain their effects on human man fertility. It has been observed that DEHP administered by gavage during gestation and lactation at high dose produced nipple retention, reduced anogenital distance, reduced testosterone formation by the fetal testis due to reduced expression of enzymes and proteins involved in steroidogenesis (Culty et al., 2008; Martinez-Arguelles et al., 2013) and caused histological changes in the testis, indicating its anti-androgen effects (Andrade et al., 2006; Ponzo and Carbone, 2013). Moreover, adult male offspring exposed *in utero* to increasing doses of DEHP showed decreased testosterone levels in presence of near normal Leydig cell numbers, so suggesting that DEHP is able to target the stem cells of the adult-type Leydig cells (Culty et al., 2008; Martinez-Arguelles et al., 2009, 2011, 2013). Low dose of DEHP administered at pre- and post-natal stage or to prepubertal and adult rat was able to induce alteration of Leydig cell development (Akingbemi et al., 2001; Ponzo and Carbone, 2013). High dose of DEHP also induced testicular malformations in the male rat offspring (Parks et al., 2000). DEHP has been shown to disrupt the androgen-regulated development of the male reproductive tract reducing absolute and relative weights of ventral prostate and seminal vesicle, altering spermatogenic processes (Dalsenter et al., 2006; Ponzo and Carbone, 2013). Moreover, perinatal exposure to DEHP induced a significant incidence of reproductive malformations in male pups such as reduced anogenital distance and testis weights (Gray et al., 2000; Ponzo and Carbone, 2013). DEHP chronic postnatal exposure

strongly affected Leydig cell hormonal functions by a decrease of testosterone biosynthesis and an increase of LH and estradiol (Akingbemi et al., 2004; Ponzo and Carbone, 2013). In rats, DEHP is rapidly hydrolyzed in the gut to MEHP that is ten-times more potent than DEHP *in vitro* (Huber et al., 1996; Gupta et al., 2010; Martinez-Arguelles et al., 2013), which pass into breast milk and cross the placental barrier (Latini et al., 2003; Stroheker et al., 2005; Ponzo and Carbone, 2013). Among phthalates, DBP is a main product of phthalate esters (PAEs) and seem that the general population is exposed to disproportionately higher amounts of DBP relative to other phthalates (Blount et al., 2000; Chen et al., 2011). It has been demonstrated that DBP has anti-androgenic activity and particularly affects the neonatal-prepubertal mouse testis (Moody et al., 2013). Prepuberty is a critical time during which the foundations of adult fertility are being established (Moody et al., 2013). It has been shown that DBP increased AMH that in turn affects development and maturation of adult Leydig cells, alters their eventual number or impairs their steroidogenic capacity (Moody et al., 2013). On the contrary, MEHP increased apoptosis of germ cells and reduced expression of AMH mRNA (Lambrot et al., 2009). Several studies have shown that DBP produced marked changes in the growth and development of the male reproductive organs, including absent or deformed epididymidis, cryptorchidism, hypospadias, reduced fertility and Leydig cell adenomas (Mylchreest et al., 2000, 2002; Mahood et al., 2007; Chen et al., 2011). The hyperplasia of Leydig cells induced by DBP could be a compensatory mechanism designed to increase testicular steroidogenesis in response to levels of testosterone that are insufficient to promote normal differentiation of the male reproductive tract (Mylchreest et al., 2002; Svechnikov et al., 2010). In a study performed on adult rats, oral exposure to DBP at 250 mg/kg induced a decrease of the sperm count, an increase of the abnormal sperm percentage, an increase of synthesis of testosterone (Chen et al., 2011).

Like many EDCs, also phthalate and their metabolites have been suggested to interfere with normal steroidogenesis, suppressing the expression of steroidogenic enzymes (Moody et al., 2013), disrupting the regulation of cholesterol and lipid homeostasis or insulin signaling (Barlow et al., 2003; Liu et al., 2005; Knez, 2013). Phthalate exposure reduces testis cholesterol and cholesterol-containing lipid droplets in rat FLCs (Barlow et al., 2003; Lehmann et al., 2004; Johnson et al., 2011, 2012). Specifically, the immediate event precipitating Leydig cell testosterone attenuation appears to be the reduced expression of mRNA and protein within the cholesterol trafficking/biosynthesis and steroidogenic enzymatic pathways (Johnson et al., 2012). Urinary phthalate metabolite levels were negatively associated with testosterone levels (Pan et al., 2006; Mendiola et al., 2011), follicle-stimulating hormone (FSH) (Duty et al., 2005), and luteinizing hormone (LH) (Jönsson et al., 2005; Jeng, 2014). Particularly, PAEs and DEHP were observed to exert a direct effect on Leydig or Sertoli cell structure and function (Jones et al., 1993; Sharpe, 2001; Jeng, 2014) specifically acting on testosterone synthesis inhibition in Leydig cells (Desdoits-Lethimonier et al., 2012). It has been demonstrated that some phthalates disrupt the pattern of gene expression that regulate cholesterol and lipid homeostasis or insulin signaling inducing a decrease of testosterone synthesis (Barlow et al., 2003; Jeng, 2014). Using the Leydig cell tumor MA-10 cell line, it has been demonstrated that MEHP increases lipid droplets and decreases progesterone production (Dees et al., 2001), suggesting that cholesterol is not transported into the mitochondria for steroid biosynthesis, but rather accumulated in lipid droplets (Martinez-Arguelles et al., 2013). Similar results have been observed *in vivo* using Wistar rats with a decrease of testosterone levels and increase of testicular cholesterol content (Botelho et al., 2009; Martinez-Arguelles et al., 2013). Short-term (12-h) *in vitro* incubation of spermatozoa with the highest concentrations of phthalates detected in human semen samples through environmental exposure resulted in decreased sperm motility, whilst prolonged incubation (96 h) resulted in sperm citotoxicity (Pant et al., 2011). Studies on human fetal testis explants demonstrated a role of phthalates on human steroidogenesis with inhibition of testosterone production (Desdoits-Lethimonier et al., 2012; Knez, 2013). Moreover, Wang et al. (2006, 2007) demonstrated that *in vitro* a low dose (1000 nmol/L), MBP, an active metabolite of DBP, exhibited a stimulating effect on steroidogenesis, while exhibiting an inhibiting effect at a higher dose (800 μmol/L) suggesting an inverted U dose-response curve common to several EDCs (Chen et al., 2011). Moreover, phthalate has been shown induce sperm DNA damage. Specifically, in a US study, an association between increased sperm DNA damage and MEP and MEHP was found (Duty et al., 2003; Hauser et al., 2007; Jurewicz et al., 2013; Jeng, 2014). Human phthalate exposure levels in the general population are low as compared with the dose levels required to elicit reproductive toxicity in the rat. Although this appears to suggest a negligible human male reproductive system risk, phthalates are only one component of a mixture of chemicals to which humans are exposed. Since humans are continuously exposed to multiple combinations of compounds with anti-androgenic and estrogenic effects, it is important to assess the joint action exhibited by mixtures of chemicals that disrupt a common system or target tissue instead of chemicals sharing a narrowly defined mechanism of toxicity (Kortenkamp et al., 2007; Kortenkamp and Faust, 2010; Nordkap et al., 2012). When combined with other EDC in rats, it is clear that phthalates contribute to reproductive toxicity below the no-observed-adverse-effect level of individual phthalate congener exposures (Committee on the Health Risks of Phthalates, 2008; Johnson et al., 2012).

CONCLUDING REMARKS

Studies of the last decade strongly support that male reproductive health has been deteriorating (Diamanti-Kandarakis et al., 2009; Soto and Sonnenschein, 2010; Svechnikov et al., 2010; Si et al., 2015). Specifically, reproductive effects after developmental exposure to mixtures of environmental EDCs have been observed both shortly after birth, in puberty, and in young adulthood (Hass et al., 2007, 2012; Christiansen et al., 2012; Jacobsen et al., 2012; Isling et al., 2014). The complexity of the mechanisms involved in EDC actions means that their health effects can be the result of the action through multiple pathways, potentially leading to greater-than-additive-effects (Kortenkamp, 2007; Knez, 2013). Such interactions among different EDCs could even allow substances that would not produce any effects by themselves to produce

significant effects at concentrations present in the environment (Kortenkamp, 2007; Christiansen et al., 2012; Knez, 2013).

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