Tạp chí Công nghệ Sinh học **10**(1): 1-13, 2012

REVIEW

ENVIRONMENTAL ENDOCRINE DISRUPTING CHEMICALS: TOXICOLOGICAL RISK ASSESSMENT BY *IN VIVO* AND *IN VITRO* MODELS

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SUMMARY

Over the last 50-60 years, a growing body of evidence suggests that numerous chemicals, both natural and man-made, may interfere with the endocrine system and produce adverse effects in human and animals. Scientists often refer to these chemicals as "endocrine disruptors" These chemicals, e.g 2,2-bis-(4-hydroxyphenyl)propane (BPA), 4-tert-octylphenol (OP), 4-nonylphenol (NP), di-(2-ethylhexyl) phthalate (DEHP), Flutamide, Parabens *etc.* are found in many of everyday used products, including some plastic bottles, metal food cans, detergents, flame retardants, food ingredients, toys, cosmetic consumer products, pharmaceutical preparations and pesticides. Although, human may expose to endocrine disruptors through food and beverages they consume, medicine they take, and cosmetics they use, limited scientific information is available on the potential adverse human health issues Further investigation is needed to elucidate in greater detail the adverse effects of environmental endocrine disrupting chemicals on the epidemiology, immunology, pathology and molecular biology in order to provide a robust and reliable assessment to consumers prior to the direction in the use of several products in their life

Keywords: *Endocrine disruptors, BPA, OP, NP, DEHP, Flutamide, Parabens, Estrogenicity, Androgenicity.*

GENERAL BACKGROUND

Endocrine disruptors can mimic or partly mimic naturally occurring hormones in the body, i.e., estrogen (a female sex-steroid hormone) and androgen (a male sex-steroid hormone) and thyroid hormone, potentially produce detrimental effects, or bind to a receptor within a cell and block the endogenous hormone activities. Many of these chemicals have been involved in developmental, reproductive, neural, immunological, and other problems in wildlife and laboratory animals. These chemicals have also been referred to as endocrine modulators, environmental hormones, and endocrine active compounds. Hormones are produced by the endocrine tissues, such as ovaries, testes, pituitary, thyroid and pancreas, and then secreted into the blood to act as the body's chemical messengers where they direct communication and coordination among other tissues throughout a body. For instance, hormones work with nervous system, reproductive system, kidneys, gut, liver and fat to help maintain and control: body energy levels, reproduction, growth and development, internal balance of body called homeostasis, responses to surroundings, stress, and injury. Endocrine disruptors may interfere with body's own hormonal signals because of their structure and activity. Environmental chemicals with an estrogenic activity are probably the most well studied, however the chemicals with anti-estrogen, androgen, anti-androgen, progesterone, or thyroid-like activity have also been identified. Although there is little evidence to prove that low-dose exposures cause adverse effects on human health issues, a large body of research in experimental animals and wildlife suggests that endocrine disruptors may cause reductions in male fertility and declines in the numbers of males born, abnormalities in male reproductive organs, female reproductive diseases including fertility problems, early puberty, and early reproductive senescence, increases in mammary, ovarian, and prostate cancers.

SUMMARY OF *IN VITRO* AND *IN VIVO* STUDIES ON THE ANTIANDROGENICAL ACTIVITIES OF DI-(2-ETHYLHEXYL) PHTHALATE (DEHP) AND FLUTAMIDE

Moreover, a large group of environmental pollutants, are believed to act as agonists or antagonists of androgens and estrogens, which are key hormones involved in many physiological processes. These pollutants have been linked to male reproductive defects in humans, including an

increase in the incidence of testicular cancer (Forman, Moller, 1994), and declining semen quality (Andersen *et al.*, 2000). In addition, EDs have been linked to developmental problems in the testis and reproductive tract, including reductions in fertility and litter size, induction of cryptorchidism and testicular atrophy (Fisher *et al.*, 2003; Mylchreest *et al.*, 2000). Adverse trends in human and animal male reproductive health, particularly with regards to the regulation of environmental factors, suggest that future generations will be at greater risk. Previous reports have suggested that male reproductive system disorders, which often originate during the fetal stage, can appear as testicular dysgenesis syndrome (TDS) after birth (Sharpe, 2001).

Recently, environmental, anti-androgenic compounds have been recognized as endocrine disruptors (EDs) because of their hormone-like activities (i.e., thereby stimulating an androgen-dependent response). Anti-androgenic chemicals have the potential to interfere with male reproductive development and function in humans and animals. The EDs are thought to act via many mechanisms, including: decreasing androgen synthesis, exerting effects on the pituitary-gonadal axis and/or blocking the androgen receptor (AR). The consequences of these actions may cause abnormal hormonal regulation and gene expression. It has been demonstrated that the AR plays a critical role in the control of male sexual differentiation. During mammalian sex differentiation, the androgens, testosterone (T), and its metabolite, dihydrotestosterone (DHT), produced by the fetal/neonatal male during sexual differentiation, are critical factors in the male phenotype (Wilson, Tarttelin, 1978). Sex development continues postnatally with the onset of secondary sexual characteristics at puberty, and the acquisition of reproductive capacity. In addition, the differentiation of the Wolffian structures (e.g., the epididymis, vas deferens and seminal vesicles) appears to be T-mediated, while masculinization of the prostate and external genitalia are controlled by the more potent androgen DHT. These developmental events may be influenced by ED-exposure via an AR-mediated mechanism in which the ED acts either as a hormone agonist or antagonist (Gray *et al.*, 2000).

A variety of chemicals present in the environment have the potential to interfere with the normal function of the endocrine system. While there is good agreement that these compounds may induce reproductive, developmental and behavioral changes at high doses in experimental animals, a discussion still persists about whether low, human and environmentally relevant, doses may also contribute to the induction of disorders in humans and wildlife (Andrade *et al.*, 2006; Daston *et al.*, 2003). In fact, androgen deficiency caused by exposure to antiandrogens during critical stages of development results in various sexual aberrations in male animals, including a decrease in the anogenital distance (AGD), an increase in nipple retention, an underdevelopment or absence of reproductive organs, malformed external genitalia (hypospadia), undescended testes (cryoptorchidism) and decreased sperm concentration (Gray *et al.*, 1994; Mylchreest *et al.*, 1998; Ostby *et al.*, 1999; You, Sar, 1998).

Experiments on developmental toxicity of di-(2-ethylhexyl) phthalate (DEHP) and potential risk assessment

Phthalates are well-known as reproductive toxicants in mammals. The toxic effects of this ED class on the reproductive system have been observed in many previous studies. And, recent reports demonstrate the ability of these compounds to disrupt the sexual differentiation of the male fetus (Gray *et al.*, 2000; Mylchreest *et al.*, 2000). The spectrum of effects induced by prenatal exposure to activated phthalates like di(butyl) phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) are believed to arise from disruption of Sertoli cell and Leydig cell functions in the developing testis (Fisher *et al.*, 2003; Sharpe, 2001). The consequences of high dose, maternal phthalate exposure include reduced anogenital distance, retained nipples, undescended testis, hypospadias, small accessory sex glands and epididymal and testicular abnormalities; all of which have been observed in male offspring rats (Gray *et al.*, 2000; Moore *et al.*, 2001; Mylchreest *et al.*, 1999). A number of these reproductive tract anomalies are characteristic of disturbances in androgen-dependent development. In addition, disturbance of normal gonocyte development resulting in multinucleated cells and subsequent changes in testicular function (e.g., reduced sperm production) have been associated with abnormal Sertoli cell function and proliferation (Fisher *et al.*, 2003; Li *et al.*, 2000). Di-ethylhexyl phthalate (DEHP) was widely used as a plasticizer in commercial products (Kavlock *et al.*, 2002). The effects of DEHP on male reproductive development have been well studied in rats (Andrade *et al.*, 2006).

In addition, phthalates and their metabolites can be released from such products and have been detected in the environment (Kolpin *et al.*, 2002), posing potential health risks for humans and wildlife. Infants may be exposed to phthalates in the womb (Silva *et al.*, Feb), via breastfeeding (Mortensen *et al*, 2005) or from medical devices in neonatal intensive care units (Green *et al.*, 2005). Although DEHP has been reported to modulate fetal testosterone production (Borch *et al.*, 2006), testicular physiology, and mammalian reproduction and fertility (Supornsilchai *et al.*, 2007), the exact mechanisms by which DEHP exerts detrimental effects on body have not yet been fully elucidated. Previous studies have demonstrated the adverse effects of DEHP on the hypothalamic-pituitary-gonadal axis in neonatal female rats, as well as on ex vivo steroidogenesis in granulosa cells (GCs) and secretion of LH by gonadotropes (Svechnikova *et al.*, 2007). Moreover, exposure to phthalates during reproductive tract development reduced the number of Sertoli cells (i.e., the major somatic cell type, which supports spermatogenesis) (Sharpe *et al.*, 2003). In addition, DEHP and its metabolites decreased testicular testosterone levels in rodents (Jones *et al.*, 1993), suggesting potential impacts of these contaminants on Leydig cells. A recent study indicated that a variety of steroidogenesis related genes were altered following phthalate- exposure and a down-regulation of most of genes involved in testosterone (T) biosynthetic pathways was observed, indicating the potential mechanism for decreased T synthesis induced by phthalate exposure (Barlow *et al.*, Jun). Other study has reported a similar genetic response in the fetal and prepubertal testes of rats exposed to these environmental chemicals (Lahousse *et al*, 2006).

The potential adverse health effects of Flutamide

Other chemicals such as Flutamide (FLU) are non-steroidal antiandrogens that inhibit androgen uptake and/or nuclear binding of androgen in target tissues. This chemical is well known as a potent AR antagonist, having been widely used in studies of male reproductive development. It has been demonstrated that pre- and postnatal FLU exposure to rats may alter androgen-dependent reproductive development and function (Imperato-McGinley *et al.*, 1992; Kassim *et al.*, 1997). FLU chemicals exposure also increases plasma LH levels and stimulates intracellular steroidogenesis in rat testes. In addition, lower ventral prostate and seminal vesicle weights have also been reported, suggesting that FLU exerts anti-androgenic effects on androgen-targeting organs (Mathur, Chattopadhyay, 1982). It has been indicated that exposure of rats to FLU caused a dysregulation in expression of hypothalamus/pituitary hormone genes and consequently this may affect gonadotropin release and induce an over-expression of testicular steroidogenic enzyme genes (Ohsako *et al.* 2003). Recently, investigators have reported adverse trends in male reproductive health, including an increasing incidence of testicular cancer (Forman, Moller, 1994), low and probably declining semen quality (Andersen *et al.*, 2000) and increasing incidences of cryoptorchidism, i.e. undescended testis, and hypospadias (Paulozzi *et al.*, 1997; Toppari *et al*, 1996). Both the increased incidence of testicular cancer and decreased sperm quality have shown a birth-cohort effect (Bergstrom *et al*, 1996; Irvine, 1994), indicating that there are more problems in younger generations. Additionally, it has been proposed that all of these disorders have a common origin in fetal life, and thus, they all represent different symptoms of the same underlying entity called the testicular dysgenesis syndrome (TDS) (Asklund *et al.*, 2004; Sharpe, 2003). A previous animal study also demonstrated the potential impact of these compounds on the male reproductive system during the "critical window" of development in a rat model. FLU chemicals were altered in gene expression in the testes and exerted distinct anti-androgenic effects on the male reproductive system (Vo *et al.*, 2009). The consequences of ED exposure need to be investigated to elucidate the mechanisms underlying their adverse effects on the reproductive, neurological and immunological systems.

RISK ASSESSMENT OF ENDOCRINE ACTIVE ESTROGENIC COMPOUNDS: BISPHENOL A (BPA), 4-TERT-OCTYLPHENOL (OP), 4-NONYLPHENOL (NP), AND PARABENS

Environmental Bisphenol A (2,2-bis-(4-hydroxyphenyl)propane BPA) chemicals impacting brain development, cancer risk, reproductive and developmental endpoints

Some man-made chemicals mimic the hormones naturally made by the body or disrupt normal hormonal actions. One of the most prominent xenobiotic estrogens, frequently called xenoestrogen, is Bisphenol A (BPA, 2,2-bis-(4-hydroxyphenyl)

propane) (Committee on Hormonally Active Agents in the Environment, 1999). Bisphenol A is an industrial chemical used in the manufacture of polycarbonate plastic and epoxy resins. Bisphenol A is used in numerous consumer products, including food and water containers, the inside lining of cans, in some types of baby bottles, an in some dental fillings (Welshons *et al.*, 2006). The pollution of BPA into food or water from plastic containers has been influenced by the manufacturing process, storage conditions, and heating by users (Howdeshell *et al*, 2003; Hunt *et al.*, 2003). In one study, BPA was detected in polycarbonate baby bottles after dishwashing, brushing, and boiling. Levels of BPA detected in liquid held in 12 polycarbonate baby bottles exceeded 8μg/L after 51 washing cycles (Brede *et al.*, 2003). Some brands of dental sealants, commonly applied by dentists to protect teeth, contain BPA, and may be a source of exposure to BPA at concentrations that show health effects in rodents (Joskow *et al.*, 2006). These chemical components used in these increasingly chemically complex products have been shown to possess the principle adverse health effects. More recent studies continue to show the effect of exposure to BPA on alterations in brain development, specifically, in laboratory animals altered sexual differentiation, accelerated puberty, and altered reproductive cycle (Maffini *et al*, 2006). BPA has been found to mimic the actions of estrogen in developing neurons, resulted in alterations in the regions of the brain associated with sexual differentiation. Low doses of BPA can disrupt important effects of hormones in the developing brain, and associate with impaired learning and memory (Kamrin, 2004; MacLusky *et al.*, 2005). Like an estrogen hormone, BPA is critical cues for brain development, so is the receptor to which hormones bind to effect cellular changes. BPA modulates the receptor of somatostatin, a hormone that inhibits the release of growth hormone, thyroid stimulating hormone, and insulin. BPA altered the expression of brain somatostatin receptors at 400 μg/kg/day of BPA (Facciolo *et al.*, 2002). Low-dose exposure to BPA increased progesterone receptor RNA message levels at 400 μg/kg/day (Funabashi *et al.*, 2003). Aloisi et al (2001), noted changes in estrogen receptor RNA levels at 40 μg/kg/day of BPA (Aloisi *et al.*, 2001; vom Saal *et al.*, 2005), whereas Ramos et al. (2003) noted changes in estrogen receptor RNA at 25 μg/kg/day of BPA (Ramos *et al.*, 2003). On the other hand, BPA has been shown to alter the expression of receptors that are involved in regulating the brain control systems that coordinate the functioning of the reproductive system as well as reproductive and other social behaviors. Several studies show that low-dose exposures of adult male rats, at levels between 0.2 and 20 μg/kg/day reduce daily sperm production and fertility (Al-Hiyasat *et al.*, 2002; Chitra *et al.*, 2003a; Chitra *et al.*, 2003b). Male rats were administered low-doses of BPA, which exhibited decreased sperm count, decreased testicular and epididymal weights, and increased prostate weights (Chitra *et al.*, 2003a). In the studies by Al -Hiyasat AS (2002) and vom Saal F (1998) male mice given extremely low doses of BPA also exhibited reduced sperm production (Al-Hiyasat *et al.*, 2002). Altered hormone levels may be associated with changes in sperm production. BPA has been reported in concentrations of 2μg/kg/day that decreased plasma testosterone in maternal rats (Akingbemi *et al.*, 2004; Kawai *et al.*, 2003). Moreover, maternal low-dose exposure to BPA was correlated with increased in prostate size due to hyperplasia (cell overgrowth) in the male mouse offspring (Gupta, 2000; Timms *et al.*, 2005) Additionally, exposure to BPA during fetal development was also shown to increase susceptibility to prostate cancer in male rats later in life (Ho *et al*, 2006). The especially results in 15 laboratories were shown that extremely low doses of BPA initiated the growth of human prostate cancer cells (Wetherill *et al.*, 2002). Although BPA is thought to increase cancer risk, it does not do so in the "normal" way- bisphenol A alters the way that key segments of DNA are translated into proteins that control how cells function. This important new area of research raises questions regarding exposures during critical windows of development (Herman, 2005). Recent studies show that low-dose BPA exposure stimulates mammary gland development (Markey *et al.*, 2001), and that prenatal exposure to BPA causes long-lasting changes in female rat breast tissue (Durando *et al.*, 2007). Animals exposed in uteri to BPA have a significantly higher sensitivity to estradiol (a form of estrogen- one of the main risk factors for breast cancer), and which is another breast cancer risk factor for humans (Munoz-de-Toro *et al.*, 2005). The exposure a single dose of BPA at levels currently found in humans can result in altered levels of blood glucose and insulin, and twice-daily exposure for just four days results in insulin resistance. In short-term exposure to BPA at doses close to, or below the current reference dose (presumed to be safe for humans), changes blood glucose levels and shown to alter important cell

signaling processes in pancreatic cells, which may help explain why BPA is associated with insulin resistance in adult mice (Alonso-Magdalena *et al.*, 2006). Additionally, the effects of BPA on weight gain and fat metabolism are of interest, but for now continue to be speculative. There is a complex relationship between fat cells, blood glucose levels and insulin. Glucose can be converted to starch and stored in the liver, or it can be converted to fatty acids and stored in fat cells. Fat cells produce chemicals that can block the function of insulin resulting in insulin resistance. BPA has been shown to increase glucose uptake in the fat cells of mice, which could be related to the development of insulin resistance (Sakurai *et al.*, 2004). The concern is that BPA can interfere with neurological development in such a way that influences behavior. Several studies have demonstrated that low-dose exposure to BPA causes behavioral effects in laboratory animals, including hyperactivity in rats (Ishido *et al.*, 2004) increase in aggression in mice (Farabollini *et al.*, 2002; Funabashi *et al.*, 2003), changes in response to painful or fear-provoking stimuli (Aloisi *et al.*, 2002) reversal of normal sex differences in the brain structure and elimination of sex differences in behavior (Negishi *et al.*, 2004) decreased maternal behavior such as reductions in time spent nursing, increases 16 in time out of the nest and away from offspring (Kubo *et al.*, 2003) altered play and other socio-sexual behaviors (Aloisi *et al.*, 2002; Dessi-Fulgheri *et al.*, 2002) and increased susceptibility to drug addiction (Adriani *et al.*, 2003). Several studies suggest an association between exposure to low doses of BPA and miscarriages in women. Scientists examined patients who had suffered three or more consecutive miscarriages and compared the blood BPA levels to women who had no previous miscarriages. The results indicate that women with multiple miscarriages had three times the level of BPA in their blood than women who had never miscarried (Sugiura-Ogasawara *et al.*, 2005). In another study, women who had polycystic ovary syndrome (PCOS) had higher levels of BPA, were more obese, and had higher levels of male sex hormones, including testosterone and androstenedione (Takeuchi *et al.*, 2004). In addition, low-dose exposure to BPA may influence the timing of the onset of puberty. Several studies in laboratory animals reveal the early onset of sexual maturation in females occurring at maternal doses between 2.4 and 500 µg/kg per day (Honma *et al.*, 2002; Nikaido *et al.*, 2004). Besides, BPA provided to rats at doses ranging from 1- 50 mg/kg/day during pregnancy and lactation was associated with an increase in serum total T4 (the thyroid hormone thyroxine) in pups on postnatal day 15, although T4 concentrations appear to be equivalent to controls by postnatal day 35 (Zoeller *et al.*, 2005). In an earlier study, the ability of BPA to bind thyroid hormone receptors were demonstrated (Moriyama *et al.*, 2002). These studies suggest that mechanisms of endocrine disruption beyond altered estrogen or testosterone regulation must be considered. In fact, recent studies of BPA focusing on reproductive and developmental endpoints, have identified adverse effects at exposure doses that are lower than what is considered to be a safe dose both in the United States and in Europe. According to the CDC, 95% of Americans have detectable levels of BPA in their bodies (Calafat *et al.*, 2005). In present, the observed BPA levels detected - 0.1 to 9 ppb were at and above the concentrations known to reliably cause adverse effects in experiments with laboratory animals. The ubiquitous use of BPA provides great potential for exposure of both the developing fetus, indirectly through maternal exposure, and the neonate, directly through in gestation of tinned food, infant formula, or maternal milk (vom Saal *et al.*, 2007). Indeed, BPA has been measured in maternal and fetal plasma and placental tissue at birth in humans (Vandenberg *et al.*, 2007). Children's exposures begin at conception, as BPA, can cross the placenta resulting in chemical exposures to the fetus during critical windows of development. Importantly, children's brains and other organ systems are constantly developing, and there are certain windows of particular sensitivity to damage or disruption (Takahashi, Oishi, 2000).

Potential adverse health effects of 4-tert-octylphenol (OP) and 4-nonylphenol (NP)

Recent scientific studies have connected exposure to these chemicals with altered hormone levels, reproductive effects, and increased incidence of chronic diseases. The estrogenic properties of alkylphenols, specifically 4-tert-octylphenol (OP) and 4-nonylphenol (NP), are two other important estrogenic EDCs. These compounds may also be potentially harmful to exposed humans and the environment at large (Soto *et al.*, 1991). Alkylphenols (APs) have been largely used in industrial, agriculture, and domestic applications. These are frequently detected in wastewater and sewage sludge (Kolpin *et al.*, 2002), and known to be hormone disruptors. Soto *et al.* (1991) reported

that polystyrene tubes used in routine laboratory procedures release a substance with estrogenic properties. This substance was identified as a nonylphenol (Soto *et al.*, 1991). Other alkylphenols are used as antioxidants in the plastic industry and have been reported to leach from plastics used in food processing and packing (Junk *et al.*, 1974). Lopez- Espinosa *et al* (2009) was detected NP (100%) and OP (23.5%) levels in a women living in Southern Spain (Lopez-Espinosa *et al*, 2009). NP and OP are also known to have endocrine disrupting effects on fish (medaka, Oryzias latipes), so it is important to know the concentrations of APs in the environment. Because the analytical characteristics of these compounds depend on the length of the ethoxy chain, it is necessary to use appropriate compounds as internal standards or surrogates (Yoshida *et al.*, 2007). In CHO-K1 cell line experiment, Tayama *et al*, 2008 was studied for NP, OP genotoxicity, and suggested that these compounds cause repairable DNA damage (Tayama *et al.*, 2008). In addition, OP and NP were reported to bind directly to the ER in trout, stimulate citelogenin gene expression in trout hepatocytes, be mitogenic in MCF-7 cells and stimulate transcription in mammalian cells via ER. *In vitro* studies revealed that OP and NP are the most potent estrogenic alkylphenols, and the potency of OP has been shown to be approximately 10^{-3} ~10^{-7} relative to 17β-estradiol (Safe *et al.*, 2001; Soto *et al.*, 1995). *In vitro* assays, E2 has been demonstrated to induce maximal proliferation of MCF-7 cells at 1 nM concentration, and OP and NP have been found to be considerably potent compounds as estrogenic chemicals at 1 and 10 μM, respectively. Treatments with OP and NP inhibited the binding affinity of E2 to ER in MCF-7 cells by a competitive ER binding assay (Kwack *et al.*, 2002). The determination of NP, OP in water has become an increasingly importance activity due to increase knowledge about their toxicities, even at low concentration. In water samples from the reclaimed water plant of Tianjin, northern China, were identified some EDs, include NP, OP. Their concentration ranged from below the limit of detection (LOD) to 8.1 ng L(-1), from <LOD to 14.2 ng L(-1), and from 1.00 microg L(-1) to 23.8 microg L(-1), respectively. The average removal efficiencies for target EDCs varied from 30% to 82%. These results indicate that environmental endocrine disrupting compounds are not completely removed during reclaimed water treatment and may be carried over into the general aquatic environment. Thus EDs into the environment can lead to serious human health problems and can affect plant and aquatic organisms (Wang *et al.*, 2005). In animal experiment, treatment with OP had significantly lower ovarian weights, higher uterine weights, and vaginal opening was observed to have occurred several days prior to that of the control group. A significant higher basal LH levels, persistent estrus, and a decreased number of corpora lutea and an increased number of preantral and atretic follicles was observed in OP exposure during the critical period of sexual brain differentiation (Willoughby *et al.*, 2005).

Risk evaluation toxicological effects of Parabens

A variety of studies have focused on the hormone-like activities of the environmental chemicals which are well-known as xenobiotic estrogens in the environment, especially related to the food industry or cosmetic products. They have received much attention as a possible source of certain hormonal disease states in human and wildlife. A wide range of parabens including methylparaben, ethylparaben, butylparaben, isobutylparaben, and isopropylparaben are widely used as antimicrobial agents in food ingredients, cosmetic consumer products such as underarm deodorants, antiperspirants, skin moisturizers, body creams, body sprays and suncare products, or in pharmaceutical preparations (Hossaini *et al.*, 2000). Recently, parabens have been shown to act as xenoestrogens, a class of endocrine disruptors (EDs), whose chemical structures can be closely associated with differences in their estrogenicity. It is reported that parabens possess a weak estrogenic activity (Ge, Chang, 2006; Lemini *et al*, 2003). In addition, these chemicals might cause disruption of endocrine systems, and consequently influence the growth, differentiation, function of reproductive systems. Other reports have indicated the outcome of paraben-exposure in the development of hormone dependent cancers (Byford *et al.*, 2002; Okubo *et al.*, 2001). The potential adverse effects of parabens were reported both *in vivo* and *in vitro*. Parabens may increase the risk of estrogen-mediated endpoints, including an increase in the incidence of female breast cancer, interference with male reproductive functions and an influence on the development of malignant melanoma (Darbre, Harvey, 2008). A linear relationship between parabens and cell proliferative potency, and parabens and ER-binding capacity, has been reported (Gomez *et al.*, 2005; Terasaka *et al.*, 2006). Little is known about the

long-term health risks of paraben exposure during fetal or prepubertal stage. The effects become increasingly complex with respect to the age, reproductive history, and endocrine milieu of the host at the time of exposure. In rats, most spontaneous neoplasias (with the exception of leukemia) of the endocrine organs or of organs appear to be under endocrine control. It has been concluded that mechanism-based toxicology is not yet sufficient for human risk assessment, and this approach should be coupled to, and/or validated by, traditional long-term bioassays (Russo, Russo, 1996). A few conventional short- and long-term systemic toxicity studies of parabens in animals treated orally are available, but there is insufficient information to demonstrate whether the adverse effects of parabens, seen in animals, are associated with estrogenic activity. As chemicals showing weak estrogenic activity (Routledge *et al.*, 1998), parabens can lead to a more general environmental estrogen problem. In animal uterotrophic assays, a reversible modification of the morphology and physiology of the uterus has been investigated (Kang *et al.*, 2002). Additionally, an alteration evoked by these chemicals in global patterns of gene expression caused aberrant estrogen signaling in the cells and adversely influence breast cancer development (Pugazhendhi *et al.*, 2007; Terasaka *et al.*, 2006). Using fetal rat reproductive organs, exposure to parabens also induced a dysregulation of multiple genes (Naciff *et al.*, 2003). Parabens are quickly absorbed through the skin (Darbre *et al.*, 2004), present in either human breast tissue or human milk (Donovan *et al.*, 2004). It has also demonstrated the biological and toxicological effects of parabens on reproductive, cardiovascular, skeletal, and gastrointestinal system (Henry *et al.*, 1993). Parabens are thought to be converted into p-hydroybenzoic acid by hepatic metabolism, which can be inferred from the detection of phydroxybenzoic acid as the main metabolite in the blood and urine of mammals exposed to parabens (Soni *et al.*, 2005). Like all xenoestrogens, parabens can mimic the effects of the physiological estrogen. They may bind to ERs, stimulate the ER-dependent response, and/or influence the expression of estrogen-responsive genes, including estrogen receptor alpha (ERα), progesterone receptor (PR), and pS2 (Byford *et al.*, 2002; Okubo *et al*, 2001). ER dependent estrogenic activities of parabens were demonstrated in MCF-7 human breast cancer cell (Byford *et al.*, 2002; Okubo *et al.*, 2001; Pugazhendhi *et al.*, 2007), ZR-75-1 cell lines (Darbre *et al.*, 2004; Ge, Chang, 2006), rodent models (Darbre *et al*, 2003; Lemini *et al.*, 2003; Oishi, 2004) and fish (Inui *et al.*, 2003). The estrogenic potency of paraben has been shown to depend on the lengths of their alkyl side chains (Darbre *et al*. 2003; Okubo *et al.*, 2001). Additionally, the current data from ER binding assay have shown that estrogenic activities of parabens also depend upon molecular weight of each chemical. The estrogenicity of members of paraben-group, including methyl-, ethyl-, propyl-, butyl-, isobutyl-, isopropyl-, or benzyl-parabens are district when compared to 17β- estadiol (E2), a nature estrogen (Hossaini *et al.*, 2000; Lemini *et al.*, 2003). The potency of parabens as estrogens appears to depend on the lengths of their alkyl side chains (Darbre *et al.*, 2003; Okubo *et al.*, 2001) An increase in the size of the alkyl group may enhance paraben transactivation of ERs *in vitro* (Routledge *et al*, 1998). Parabens can mimic the effects of the main natural estrogen (17β-estradiol) by binding to ERs (Okubo *et al.*, 2001). Although parabens have a similar molecular structure to estrogens, the estrogenic activities of these environmental endocrine disruptors (EDs) are not clearly understood. Despite the effects of parabens on human and animal health, these chemicals are officially approved food additives in many countries. The European Union permits the use of parabens at maximum concentrations of 0.4 to 0.8% in cosmetic products (EU Cosmetics Directive 76/768/EEC) and the daily intake is 0 to 10 mg/kg/day. In Japan, the daily intake permitted is 1.06 mg per person (Ishiwatari *et al*, 2007). In the USA, the potential average daily intake is approximately 1 to 16 mg/kg for infants and 4 to 6 mg/kg for persons aged two years or older.

CONCLUSION

To date, there is little definitive data in the published literature from studies on the bioavailability, metabolism, short-term and long-term toxicity, reproductive toxicity, genotoxicity, and carcinogenicity of exogenous and/or endogenous compounds. Reports on studies in experimental animal models on the mechanisms of environmental endocrine disrupting chemicals as estrogenic/ androgenic compounds are lacking. Further research is needed to provide new insights into the mechanism(s) through which endocrine disruptors elicit their effects on biological systems and on

human and animal health. Additionally, the systemic evaluation of the EDs-induced effects on the epidemiology, immunology, pathology and molecular biology is needed in order to make the direction in the use of chemicals in our life.

Acknowledgements: *We thank the National Foundation for Science and Technology (NAFOSTED) of Vietnam for the financial support (Grant 106.06-2011.33)*

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HÓA CHẤT MÔI TRƯỜNG GÂY RỐI LOẠN NỘI TIẾT: NHỮNG ĐÁNH GIÁ RỦI RO VỀ ĐỘC TÍNH TRONG MÔ HÌNH *IN VIVO* VÀ *IN VITRO*

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Viện Công nghệ sinh học

TÓM TẮT

Trong vòng 50 - 60 năm qua, cùng với quá trình phát triển của xã hội, một bằng chứng cũng cho thấy đã xuất hiện nhiều loại hoá chất cả tự nhiên và nhân tạo, những nhóm hóa chất này có thể gây ảnh hưởng đến hệ thống nội tiết và tác động xấu đến sức khỏe con người và động vật. Các nhà khoa học thường đề cập đến các hóa chất này với tên gọi là "chất gây rối loạn nội tiết". Một số loại hóa chất như: 2,2- bis-(4-hydroxyphenyl) propan (BPA), 4-tert-octylphenol (OP); 4- nonylphenol (NP); Di-(2-ethylhexyl)phthalate (DEHP); Flutamide; Parabens...được cho phép sử dụng trong nhiều sản phẩm sinh hoạt, bao gồm các sản phẩm chai nhựa, vỏ đồ hộp kim loại, chất tẩy rửa, chất gây cháy, thành phần thực phẩm, đồ chơi, sản phẩm mỹ phẩm, chế phẩm dược phẩm, và thuốc trừ sâu. Mặc dù, con người có thể tiếp xúc hàng ngày với các chất gây rối loạn nội tiết này thông qua nhiều con đường như: thực phẩm, đồ uống, thuốc dược phẩm, nhưng những thông tin khoa học về ảnh hưởng có hại của chúng đối với sức khỏe con người còn rất hạn chế. Trong tương lai, cần thiết phải có các nghiên cứu để làm sáng tỏ các tác dụng phụ của hóa chất môi trường gây rối loạn nội tiết trong vấn đề dịch tễ học, miễn dịch học, bệnh lý học và sinh học phân tử để có thể cung cấp các thông tin chính xác, đáng tin cậy cho người tiêu dùng trước khi đưa ra quyết định trong việc sử dụng các loại sản phẩm trong cuộc sống của họ.

Từ khóa: *Gây rối loạn nội tiết, BPA, OP, NP, DEHP, Flutamide, Parabens, Hoạt tính estrogen, Hoạt tính androgen*

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