Pathophysiological Mechanisms of Endocrine Disrupting Chemicals

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Abstract: An endocrine disruptor is an exogenous substance or mixture that alters function (s) of the endocrine system consequently causing adverse health effects in an intact organism, or its progeny populations. Over 800 chemicals used in daily life possess endocrine disrupting properties. These chemicals are involved in many chronic diseases like cardiovascular problems, diabetes, obesity, reproductive abnormalities, thyroid problems, neoplasm and many homeostatic imbalances. From the atmosphere, EDCs in the vapor phase are transferred to soil surface either by physical or chemical processes. In this cycle, human and wildlife are threatened to endocrine disruption via inhalation of EDC from the atmosphere and consumption of EDC deposited in primary producers and bio-accumulated tissues of secondary consumers. EDCs exhibit genomic responses and modify transcriptional signals by inhibiting or synthesizing new proteins. EDCs also mimic endogenous steroid hormones and induce rapid nongenomic response by binding plasma membrane receptors and acting through second messenger-triggered signal cascades resulting in the changes in cellular motility, signaling processes and rapid hormonal synthesis. Strategies to alleviate the devastation that arises from these EDSc include strengthening the knowledge of EDCs, improved testing for EDCs, reducing exposures and thereby vulnerability to disease, identifying endocrine active chemicals, creating enabling environments for scientific advances, innovation and disease prevention and enhanced methods for evaluating evidences of EDCs.

Introduction

Endocrine system is a group of various glands that secrete hormones to control metabolism, growth and development in tissue, sexual and reproductive functions as well as sleep, and mood among other physiological changes. The use of synthetic chemicals by human has been increased extensively since the introduction of these chemicals. Endocrine-disrupting chemicals (EDC) are structurally diverse class of synthetic and natural compounds that possess the ability to alter various mechanisms of the endocrine system and potentially induce adverse health effects in exposed individuals and population (Henley *et al.,* 2006). According to the latest report, about 800 chemicals that are being used in daily life possess endocrine disrupting properties (WHO, 2013). Out of available EDC, only some of them have been examined. These chemicals are involved in many chronic diseases like cardiovascular problems, diabetes, obesity, reproductive abnormalities, thyroid problems, neoplasm and many homeostatic imbalances (Diamanti-kadarakis *et al*., 2009).

These substances are exogenous agents or mixtures that modifies activities of the endocrine system consequently causing unpleasant health effects in an intact organism, or its progeny (WHO-IPCS 2002).

A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations (WHO-IPCS 2002).

From the atmosphere, EDCs in the vapor phase are transferred to soil surface either by physical process or by chemical process. Physical process involves wet deposition and dry deposition while chemical process involves photolysis. Both of the process may ultimately lead to degradation or further transfer of EDC to water bodies where re-suspension or diffusion occurs; certain EDCs are adsorbed to the sediments. Bioaccumulation of persistent EDC among aquatic organisms occurs and certain EDCs are volatilized back to the atmosphere. In this cycle, human and wildlife exposure are threatened to endocrine disruption via inhalation of EDC from the atmosphere and consumption of EDC deposited primary producers and bio-accumulated tissues of secondary consumers.

Mechanism Involved In Endocrine Disruption

Human and wildlife exposure to atmospheric EDCs occur via inhalation, ingestion and dermal contact. In vivo studies predict numerous mechanisms to be involved in the disruption of the endocrine system by the activation of receptors at nanomolar (nM) levels and non-genomic pathways at micromolar (mM) levels resulting in the genomic instability and alteration in hormone feedback regulation (Iguchi and Katsu, 2008). In a biological system, the gene networks and target cell activities are controlled by hormones through the activation of nuclear receptors and by binding to the responsive elements in the promoter of target genes. Such activation of receptors is disrupted by EDCs that mimic endogenous hormones and bind to ligands resulting in conformational changes and difference in functional and regulatory activities of gene expression (Vijayanathan *et al*., 2007). Xenoestrogens such as endosulfan and nonylphenols showed similar structure dependent induction of luciferase activity in MCF-7 and MDA-MB-231 breast cancer cells transfected with a construct linked to ER α and luciferase (Wu *et al*., 2008). Apart from exhibiting genomic response, EDCs also modify transcriptional signals by inhibiting or synthesizing new proteins. EDCs mimicking endogenous steroid hormones can induce rapid nongenomic response by binding plasma membrane receptors and acting through second messenger-triggered signal cascades resulting in the changes in cellular motility, signaling processes and rapid hormonal synthesis (Watson *et al*., 2007). Membrane estrogen receptor (mER) activation causes release of Ca^{++} ions, altered prolactin secretion, cell proliferation, cellular immune response and maternal/paternal behavior (Wozniak *et al*., 2005). Interaction with cytosolic receptor activates the signal transducing molecules: cAMP, adenylate cyclase, calcium, phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB) and G-proteins (Silva *et al*., 2010).

Major Edcs: Sources, Exposure, Bioaccumulation And Health Impacts

Phthalates

Phthalates are the dialkyl or alkyl aryl esters of phthalic acid added to plastics as modulators of the properties of materials. They are used in the manufacture of polyvinylchloride (PVC) products, building materials, toys, clothing, cosmetics, perfumes, food packaging and medical appliances (Wormuth *et al*., 2006). Usually phthalates are not physically bound to the polymers making their diffusion easier out of the plastics into the environment. Release of household and industrial wastewater from production and processing units and disposal of materials are sources of phthalates occurring in the environment (Cifci and Arikan,

2013). The average total daily ambient exposure of phthalates in U.S. was estimated to be 0.27 mg d−1, through food (0.25 mg d−1), water (0.02 mg d−1) and air (0.4 μg d−1) excluding workplace and indoor air (Tickner *et al*., 1999). Phthalates were detected in gaseous phase and as particulates, both in indoor and outdoor air. Indoor air had 12.0 mg m−3 of phthalates of which diethyl phthalate, DEP (2.29mgm−3), butylbenzyl phthalate, BBP (3.97 mg m−3) and diethyl hexyl phthalate, DEHP (2.43 mg m−3) were the most abundant phthalates accounting 72% of Σ6 phthalates (Pie *et al*., 2013). Outdoor air along North Sea to Arctic had phthalates ranging 0.03–5.03 ng m−3 as particulates and 1.11− 3.09 ng m−3 in gaseous phase (Xie *et al*., 2007).

In laboratory study exposure to DEHP via inhalation, rats (Rattus norvegicus) showed increased lung and liver weight, foam cell proliferation and thickened alveolar septa with 50 mg m−3 as NOAEL (no observed adverse effect level) and 1000 mg m−3 as less serious LOAEL (lowest observed adverse effect level) (Klimisch *et al*., 1991). No inhalation minimal risk limit (MRL) was derived for DEHP due to inadequate data on inhalation exposure. The MRLs for intermediate and chronic duration oral exposure of 15–364 days were derived to be 0.1 and 0.06 mg kg−1 d−1. These MRLs were derived based on NOAEL of 5.8 and 14mg kg−1 d−1 for testicular pathology in male rats and decreased fertility in mouse (ATSDR, 2002). In human (H. sapiens) neonates, exposure to 0.001–4.2 mg h−1 for 12–30 days through artificial ventilation caused respiratory distress and pathological changes resembling hyaline membrane disease (ATSDR, 2002). Oral exposure in rat at the dose of 750 mg kg−1 d−1 in diet from the 14th day of gestation to the 3rd day of nursing resulted in testicular and epididymal atrophy, agenesis, hemorrhagic testes and hypospadias (ATSDR, 2002). Fetal death, exencephaly, open neural tubes and reduced pup size were observed in mouse (Mus musculus) exposed to 1000 mg kg−1 d−1 in diet for 2 days.

Correlating to the laboratory exposures, phthalates are found to be associated with reproductive disorders in both men and women. Phthalates in semen (0.08–1.32 mg/L) among men are related to declined semen quality and infertility (Zhang *et al*., 2006). Phthalate monoesters (monoethyl hexyl phthalate, MEHP andmonobutyl phthalate, MBP) in maternal urine excretion (24.9 and 78.4 ng L−1) and exposure of fetus to phthalates in amniotic fluid (22.8 and 85.2 ng mL−1) significantly induced anti-androgenic in male infants characterized by short anogenital distances (Huang *et al*., 2009). Exposure to phthalates in women was associated with pre-mature thelarche (96.5 ± 134.0 ng L−1), pregnancy loss

(MEHP, 377.6 ng mL−1; MBP, 255.1 ngmL−1) and other disorders such as smaller pre-ovulatory follicles, anovulation or delayed ovulation, longer estrous cycle, decreased synthesis of estradiol, decreased serum progesterone and increased serum follicle-stimulating hormone (FSH) (Chou et al., 2009; Toft et al., 2012). On the other hand, the studies about the effects of phthalates on the wildlife remain scarce; some in utero investigations found phthalates to hinder the male rat (R. norvegicus) reproductive tract development in a dose-additive manner via reducing the fetal testis hormone synthesis (Gray et al., 2006; Howdeshell et al., 2007).

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are aromatic, synthetic chemicals formed by two linked benzene rings with some or all of the hydrogen substituted by chlorine atoms. PCBs vary in appearance from oily liquids to white crystalline solids or hard non-crystalline resins. They are thermally stable, resistant to oxidation, acids, bases, and other chemical agents, and have excellent dielectric properties (D'Mello, 2003). PCBs have been used commercially since 1929 as insulating fluid in transformers, capacitors and as plasticizers in open systems comprising numerous building materials including adhesives, caulk, ceiling tiles, paints and sealants (Thomas et al., 2012). PCBs in caulk and other sealants often exceed 1% by weight and migrate from their source products creating the potential for exposure (MacIntosh et al., 2012). PCBs have high environmental persistence, resistance to metabolize in organism and tendency to accumulate in lipids which favor their ubiquitous presence in the environment. Resistance of PCB increases with chlorine percentage; less chlorinated PCBs are water soluble, volatile and biodegrade while highly chlorinated PCBs sorb strongly to particulate matter (Beyer and Biziuk, 2009). Based on the toxicity, persistence, accumulation and mechanism in binding aryl hydrocarbon receptor (AhR) similar to dioxins, 12 PCB congeners (4 non-ortho and 8 mono-ortho substituents) are classified into 'dioxin like-PCBs' (van den Berg et al., 2006). These PCBs have chlorines in a minimum of four at lateral positions (3, 3′, 4, 4′, 5, 5′) and none (non-) or only one (mono-) at ortho positions (2, 2′, 6, or 6′) of the biphenyl. The non-ortho dioxin-like PCBs bind to the AhR and causes dioxin-like toxicity in fish, birds and mammals while mono-ortho chlorinated dioxin-like PCBs cause dioxin-like toxicity in birds and mammals, not generally in fish. Laboratory exposure via inhalation in rats with less serious LOAEL of 0.009–1.5 mg m−3 increased thyroid hormones, T3 (3,3,5-triiodo-Lthyronine) and T4 (tetraiodo-L-thyronine) in serum and slightly degenerated renal tubules (ATSDR, 2000). In guinea pigs, Cavia porcellus 16% decreased

body weight and slight vacuolation was observed with less serious LOAEL of 1.5–5.4 mg m−3 (ATSDR, 2000). Oral exposure in rat with less serious LOAEL of 0.5–2500 mg kg−1 d−1 resulted in increased serum cholesterol, serum corticosterone, liver weight, adrenal weight, decreased T4 hormone, vacuolar degeneration and uterine weight. Correlating to the laboratory exposures, in humans PCB-153, 138, 180 and ΣPCB were in the concentration of 409.92, 177.63, 123.91 and 455. 61 ng g−1 lw. Its exposure at early pregnancy elevated thyroid stimulating hormone (TSH) (9.4 mL U L−1; normal value: 0.35− 3.5 mL U L−1), total thyroxine (9.0 μg dL−1; normal value: 4.5− 12.5 μg dL−1) and reduced T4 level (38.1 ng dL−1; normal value: 86− 187 ng dL−1) (Abdelouahab et al., 2013). Prenatally exposed infants to PCBs showed lower birth weight, smaller head circumference and alterations in the thyroid hormone homeostasis (Sadau et al., 2002) while exposed children showed altered neural development, cognitive, motor and learning abilities (Park et al., 2009; Roze et al., 2009).

Among wildlife, polar bears (Ursus maritimus) showed reduced ability of the immune system to combat common infections (such as influenza, Reo virus and Herpes virus), waned testosterone production in males, elevated progesterone in females, altered behavior and thyroid hormone levels (Lie et al., 2004; Sonne, 2010).

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds with two or more fused aromatic rings. Based on origin: pyrogenic PAHs are formed by the incomplete combustion of fossil fuels, forest fires and tobacco smoke; petrogenic PAHs are present in crude oil, its product, and coal (Vasudevan and Aruazhagan, 2007). PAHs enter the environment primarily through sewage, road runoffs, smelter industries and oil spills (Durand et al., 2004; Vasudevan et al., 2007; Mascarelli, 2010). The offshore PAHs enter water through oil seeps, spills and discharges from offshore oil installations (Kemsley, 2012; Mascarelli, 2010; Lavrova and Kostianoy, 2011). PAHs display relatively low water solubility and high solubility in lipids. When emitted into the atmosphere, most low vapor pressure PAHs are adsorb on particles (Johnsen et al., 2005) and are transported over long distances before to be deposited onto soil, vegetation or surface waters (Crimmins et al., 2004). PAH particulates and aerosols undergo photodecomposition by solar radiation (Hafez et al., 2008) and biodegradation by microorganisms such as Ochrobactrumsp, Enterobacter cloacae and Stenotrophomonas maltophilia (Arulazhagan and Vasudevan, 2009, 2011). In the atmosphere, PAHs can also react with free radicals, ozone, nitrogen

oxides and sulfur dioxide to yield diones, nitro and dinitro PAHs and sulfonic acids. In soil, PAHs are degraded by microorganisms producing biosurfactant, rhamnolipid e.g. Pseudomonas fluorescens NSI (Vasudevan and Aruazhagan, 2007).

In laboratory studies, mice were induced with different concentrations of 7, 12-dimethyl benz [a] anthracene; targeted organs showed susceptibility to the bone marrow, skin, lung cancer, ovarian and uterus cancer at the dosage of 20–200 µg mouse−1 d−1 (Buters et al., 2003).

Chronic exposure via inhalation in humans with serious LOAEL of 0.0001 mg m−3 reduced lung function, abnormal chest X-ray, cough and bloody vomit, throat and chest irritation (ATSDR, 1995). In golden hamsters (Mesocricetus auratus), serious LOAEL of 9.5 mg m−3 was found to be of cancer effect level (CEL), causing increased respiratory tract tumors and neoplasms of the upper respiratory tract (ATSDR, 1995).

Correlating to the laboratory exposures, epidemiologic studies have reported an increase in lung cancer in humans exposed to coke oven emission, roofing tar emissions, and cigarette smoke (ATSDR, 1995). Among wildlife, PAHs induce hemolytic anemia in oiled seabirds via oxidative attack of erythrocytes by PAH metabolites resulting in hemoglobin leakage and formation of Heinz bodies. In such case, haptoglobin and ferritin are up-regulated to sequester free Hb and iron in the circulation (Gera et al., 2007). PAHs are also associated with endocrine cancers including leiomyomas of the vagina, cervix and uterus, adrenal and thyroid tumors and mammary adenocarcinomas as found among Beluga whales (Delphinapterus leucas) of the St Lawrence estuary in Canada (McAloose and Newton, 2009).

Brominated Flame Retardants
In ancient Egypt about 450 BC, alum was used to reduce the flammability of wood, and ever since that time flame retardants have been used in various materials. The halogen containing compounds are used today as flame retardants in electronic equipment, textiles, plastics, paints and printed circuit boards (Chen et al., 2012) preventing fire eruptions by capturing free radicals (Birnbaum and Staskal, 2004). The most commonly used brominated flame retardants (BFRs) are polybrominated diphenyl ethers (PBDEs) and biphenyls (PBBs), 1, 2-bis (2, 4, 6 tribromophenoxy) ethane (BTBPE), hexabromocyclododecane (HBCD) and bisphenol-A ethers (Chen et al., 2012). BFRs are highly lipophilic with low water solubility, low vapor pressure and high bioconcentration factors (BCF) (Darnerud, 2003). In the atmosphere, PBDE partitions between the vapor and particulate phase significantly influencing the deposition, degradation, transport and subsequent fate in the environment (Chen et al., 2006a, 2006b). In the laboratory studies, exposure to lower brominated diphenyl ethers with less serious LOAELs of 3.7–202mgm−3 in rats significantly induced reversible rapid breathing, hepatocytomegaly, alveolar histiocytosis, chronic lung inflammation and the absence of corpora lutea in ovaries (ATSRD, 2004). The MRL of 0.006 mg m−3 was derived for intermediate-duration inhalation exposure to lower brominated BDEs based on NOEL of 1.1 mgm−3 which exhibited changes in thyroid hormones in rats when exposed intermittently to commercial octa BDE mixture for 13 weeks (Great Lakes Chemical Corporation, 2001). The PBBs and PBDEs with LOAELs of 3–3 000 and 1200–7780 mg kg−1 d−1 in rats decreased thyroid plasma T4 hormone, increased hepatic phospholipids, darkened kidney and adrenal glands, induced hepatocytic swelling, necrosis, porphyrin accumulation, ulcers, splenic fibrosis, hematopoiesis, lymphoid hyperplasia, liver neoplastic nodules, hepatocellular adenomas and carcinomas, follicular cell hyperplasia and granulomas (ATSRD, 2004). Correlating to the responses of laboratory studies, PBDE exposure in humans has also lead to liver toxicity, disruption of thyroid hormone levels, developmental neurotoxicity, and reproductive toxicity. In animals, only few species of large mammals have been studied; of which most are predators, expected to have highest body burdens of contaminants, as a consequence of biomagnification. The high body burdens of hydrophobic contaminant PBDE were found in animals such as seals (Phoca vitulina), porpoises (Phocoena phocoena), dolphins (Stenella coeruleoalba), whales (D. leucas) and polar bears (U. maritimus) (Noel et al., 2009). Moreover, a study of little brown bats (Myotis lucifugus) in USA revealed the highest concentrations of PBDEs ever found in any wild animal (13,000 ng g−1 lw); these were thought to be caused by the fact that the bats consumed POP contaminated insects of between 50 and 100% of their bw d−1 (Kannan et al., 2010).

Pesticides
Pesticides are substances or chemical mixture intended for preventing, destroying, repelling or lessening the damage of any pest. In India, pesticides are frequently used for agriculture and control of diseases such as malaria, filariasis, dengue, Japanese encephalitis, cholera, and so forth (Neelam et al., 2013). The fate of pesticides in soils with a different cropping land use has been extensively studied worldwide including India (Senthil Kumar et al., 2009). Pesticides enter the soil by direct treatment or being washed off from the plant surface during rainfall. They are relatively hydrophobic, resistant to degradation, and able to accumulate in soils and sediments (Hu et al., 2010). Recently, the widespread

contamination and toxicity of synthetic organic pesticides have become a serious environmental problem. The use of pesticides has led to increased agricultural production but in the meantime induced adverse effects on the human health and environment (Ejaz *et al*., 2004). More than 120 endocrine disruptive pesticides are known, covering numerous chemical classes (McKinlay *et al*., 2008; Faniband *et al*., 2014).

The bioaccumulation of pesticides has been widely studied in wildlife and humans which mainly depends on the inhalation and consumption of meat, fat, vegetables, green leaves and pesticide contaminated water. In a study, hexacholorobenzene (HCB) was detected in nestling bald eagle (H. leucocephalus) plasma from four areas in southwestern British Columbia and one site in California. The detected mean concentrations were 0.20, 0.26, 0.35, 0.31, and 0.08 µg kg−1 ww, for Central Fraser Valley, Lower Fraser Valley, Nanaimo/Crofton area, Barkley Sound, and Santa Catalina Island, respectively (Cesh *et al*., 2008). HCB in the follicular fluid of cattle, sheep, goats, and pigs from local farms in Greece was at the mean concentrations of 1.77, 1.25, 1.63, and 0.78 ng mL−1, respectively (Kamarianos *et al*., 2003). Human exposure to HCB was analyzed among farmers and their spouse. The mean concentration in serum ranged between 0.12–0.26 and 0.05–0.24 ng mL−1 for those from Iowa and b0.05–0.15 and 0.16– 0.17 ng mL−1 for those from North Carolina (Brock *et al*., 1998). Workers at a new hazardous waste incinerator in Constanti, Spain had mean plasma levels of HCB ranging 19.4–854.0 µg kg−1 lipid with mean as 152 µg kg−1 lipid (Domingo *et al*., 2001). In rats, the inhalation exposure to HCB at less serious LOAEL of 33–35 mg m−3 led to slight impairment of pulmonary immune defenses. In pigs (Sus domesticus), 90 day exposure to less serious LOAEL of 50 mg kg−1 d−1 of HCB retarded the development of the testis. In monkeys (Macaca fascicularis), less serious LOAEL of 1– 10 mg kg−1 d−1 for 90 days led to increased length of menstrual cycle, decreased serum progesterone level and ovulatory levels of estradiol and degenerative lesions in oocytes (Foster *et al*., 1995). Correlating to laboratory exposures, in humans OCPs are associated with a variety of adverse pregnancy outcomes, including miscarriage, preeclampsia (characterized by hypertension during pregnancy), intrauterine growth retardation (IUGR), poor weight gain during fetal development, and preterm delivery (Stillerman *et al*., 2008; Slama and Cordier, 2010). Other effects include cancer, neurological damage, immune suppression, birth defects and endocrine disruption (Wang *et al*., 2008). In wildlife, signs of endocrine disruption such as gonadal abnormalities and the feminization of males, interference with metamorphosis, changing behavior and retarded development are frequently found among frogs and toads (Hayes *et al*., 2010a, 2010b).

Dioxins

The lemma dioxins are commonly adopted to mean 210 organic chemicals, among which 75 congeners are polychlorinated dibenzo-pdioxins (PCDDs), and 135 are polychlorinated dibenzo-furans (PCDFs). Prior to industrialization, low concentrations of dioxins existed in nature due to natural combustion and geological processes; e.g. wood rotting fungi and some mushrooms which break down lignin with chlorinating and oxidizing compounds, forming dioxins (CPCB, 2007). Chlorines also improve the resistance to decomposition and solubility in lipids (Webster and Mackay, 2007), which allow them to persist in the environment and bioaccumulate (Letcher *et al*., 2010). Depending upon the capability to bind Ah receptors, elicit toxic response, persist and accumulate in the food chain; dioxins are affirmed to TEF for risk assessment in humans and mammals (EPA, 2010) In humans, out of 15 breast milk samples collected from primiparous women of Taranto, Southern Italy, 4 breast milk samples had far above the legal limit of human consumption, 3 pg g−1 (Bianco *et al*., 2013). Similar to this study, human milk samples analyzed from Faroe Island had 4.3–13.0 pg g−1 dioxins (Fangstrom *et al*., 2005). Occupational exposure being a significant source, workers involved in trichlorophenol production had elevated TCDD blood levels, with the mean concentration of 332 µg L−1 (Papke *et al*., 1992). Workers with chloracne and other illness were accidently exposed 32 years earlier and had 49 pg g−1 lw of TCDDs (Schecter and Ryan, 1988). Laboratory studies suggest TCDD MRLs of acute, intermediate and chronic oral exposure to be 0.005, 0.0007, 0.000001 µg kg−1 d−1. The corresponding MRLs were derived based on NOAEL of 0.005, 0.0007 and LOAEL 1.2×10^{-4} of µg kg−1 d−1 (Burleson *et al*., 1996; DeCaprio *et al*., 1986; Schantz *et al*., 1992). MRL for inhalation exposure was not derived due to insufficient data in humans and mammals.

In male rats, decreased testis descent, sperm production, testosterone and masculine sexual behavior in male offsprings were observed. In correlation to the laboratory exposures, dioxins cause choking of the lungs, increases susceptibility to breast cancer (CPCB, 2004; Dai and Oyana, 2008), mood alterations, reduced cognitive performance, diabetes, changes in white blood cells, dental defects, endometriosis, decreased male/female ratio of births and decreased testosterone and (in neonates) elevated thyroxin levels (CPCB, 2007). Short term exposure to

high levels of dioxin is suspected to cause chloracne, other related skin disorders, immune system toxicity, gastrointestinal ulcers, and neurotoxic effects. Long term exposures even at low concentrations may alter reproductive functions including congenital and neonatal development abnormalities (CPCB, 2004). Among wildlife, dioxins are EDCs with crucial impact on reproduction in a wide range of species (Mocarelli *et al*., 2011).

Alkylphenol

Alkylphenol polyethoxylate compounds (APEs) are widely used as non-ionic surfactants in detergents, pesticides, herbicides, emulsifiers, paints, cosmetics, plastic wares and even in jet fuel (Cevdet *et al*., 2009). They are commonly found in wastewater discharges and effluents from sewage treatment plants (Chen *et al*., 2006a, 2006b). In sewage treatment plants, APEs are degraded aerobically with sequential cleavage of ethyl moieties to alkylphenols (APs) (Kayama *et al*., 2003). APs bind strongly to soil followed by the application of sewage sludge to agricultural land and the aerobic degradation by microorganisms such as Bacillus cereus, Arthrobacter sp., Bacillus licheniformis, Halomonas salina, Bacillus pumiolus and Pseudomonas aeruginosa (Gayathri and Vasudevan, 2010) takes place. Nonylphenol (NP) is the most abundant derivatives of APEs demonstrated to stay biologically active for a longer period of time in the body than an endogenous estrogen (Brown and Reinhard, 2003). NP competes with estrogen and bind to estrogen receptor affecting reproduction and development (Colborn *et al*., 1993). Medaka (O. latipes) exposed to NP concentrations N11.6 µg L−1 had increased hepatic vitellogenin levels, altered sex ratios in off springs, formed testis, ova, decreased fecundity, fertility and ratio of motile spermatozoa (Hara *et al*., 2007). NP exposures were also associated with increased intersex frogs, altered sex ratios, and increased gonadal development (Mackenzie *et al*., 2003).

In laboratory studies, oral exposure to NPs in rats (R. norvegicus) induced decreased epididymal sperm density, increased estrous cycle length, decreased ovarian weights and accelerated vaginal opening in pups with NOAELs and LOAELs of 13–19 and 43–64 mg kg bw−1 d−1 (Cal/EPA, 2009). In Japanese quail (Coturnix japonica) embryos, 10 µg g−1 egg increased the disappearance of the lymphoid cells from the lymphoid of the bursa. In the female embryos, 100 µg g−1 egg decreased the height of simple cuboidal epithelial cells surrounding the thyroid follicle and in the male embryo, its follicle-like structure in the thymus increased (Razia *et al*., 2006). Correlating to the human exposure, NPs tend to affect estrogen responsive tissues such as the testis in males, and mammary glands and placentas in females.

In a longitudinal study of fetal exposures to EDCs in Japan, NP was detected in the umbilical cords, and evidence showed puberty in prenatally exposed boys and girls occurred at an earlier age (Mori, 2000).

Perfluorinated Chemicals

Perfluorinated chemicals (PFCs) are synthetic compounds characterized by long, fully fluorinated carbon chains with different functional head groups which enable them to strongly resist to degradation (Fromme *et al*., 2009). PFCs are used in a variety of products to resist to grease, oil, stains, and water, and are also used in fire-fighting foam (Bjorklund *et al*., 2009). PFC contamination in the environment originates from direct or indirect anthropogenic sources. Direct sources include manufacture and use of perfluoroalkylated acids (PFAAs), whereas indirect sources include product impurities and production of chemicals that may degrade to PFAA (Prevedouros *et al*., 2006). In the atmosphere, the volatile and neutral PFC precursors are transported by air masses over long distances before or while they are degraded to more persistent PFAA such as perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) (Ellis *et al*., 2004). When PFAA enter aquatic phases in the environment, they are likely to travel long distances by transport with oceanic currents to remote areas like the Arctic (Armitage *et al*., 2006) and tend to accumulate in Arctic mammals (Lau *et al*., 2007; Yamashita *et al*., 2005). In laboratory studies, female rats exposed to PFOA via inhalation to less serious LOAELs of 10–25 mg m−3 showed 18% increased liver weight and 12% decreased weight gain on gestational days 6–10. In male rats, 7.6mgm−3 increased liver weight, induced hepatocellular hypertrophy and necrosis; 84 mg m−3 resulted 7% body weight loss by the 5th day of exposure, 380–18,600 mg m−3 induced red nasal discharge, dry rales, lacrimation, reddening of eyes, corneal opacity and corrosion, stomach irritation, liver enlargement, pulmonary edema and excessive salivation (ATSDR, 2009). Oral exposure of Rhesus monkeys with less LOAEL of 10–30 mg kg−1 d−1 induced hypoactivity, prostration, emesis, increased liver weight and decreased serum total T4 (TT4) and free T4 (FT4) (ATSDR, 2009). Correlating to the laboratory exposures, PFC exposure in humans was associated with abnormal enlargement of Leydig cells and adenomas raising the concern of infertility in men (Vested *et al*., 2014). Due to occupational exposure, workers in PFOS manufacturing facility with 1–2 µgmL−1 PFOS in serum experienced higher T3 levels and increased risk of bladder and prostate cancer (Alexander *et al*., 2003; Olsen *et al*., 2003). Increased risk of infertility and irregular menstrual cycle was also observed among women with higher levels of PFOA and PFOS in serum (Fei *et al*., 2009).

Chemical and Bio-analytical Tools for EDC Detection

Biosensor technology

Bio-sensing technology started to be addressed as an emergent industry with high-potential growth mainly due to its wide range of applications and the continuously increase of assays feasibility. Furthermore, new developments in material sciences and genetic engineering laid a foundation to solve significant custom-tailored detection issues, as those raised by EDCs assessment, by improving response specificity and methods sensitivity of biosensors. (Viviana *et al.,* 2016).

***In vitro* bioassays and combined arrays**

In vitro bioassays can complement chemical analysis for screening purposes enabling measurements of biological endpoints in a sample. This achievement allows to reveal the presence of active compounds not detectable by a compositional analysis, and to identify new contaminated sites (Viviana *et al.,* 2016).

Chromatographic techniques

The most widely used methods for the determination of various EDCs are high- performance liquid chromatography (HPLC), liquid chromatography coupled with electrochemical detection (LC-ED), liquid chromatography coupled with mass spectrometry (LC-MS), capillary electrophoresis (CE), gas chromatography (GC), and gas chromatography coupled with mass spectrometry (GC–MS). Other methods such as HPLC with fluorescence or diode array detection are less frequently used in the analysis of EDCs (Viviana *et al.,* 2016).

Initiative Steps to Control the Exposure to EDC

The advances in understanding of EDCs have been based mainly on information derived from studies in developed regions. There is still a major lack of data from large parts of the world, particularly from Africa, Asia and Central and South America (UNEP/WHO, 2013). The rising needs and lifestyle indicates the increasing burden of the endocrine diseases across the globe most likely affecting the future generation. Based on the future needs to prevent and control the body burdens and diseases, and improve the health of wildlife and humans, UNEP/WHO (2013) has identified the following initiative steps:

(1) Strengthening the knowledge of EDCs: It is a critical time to understand the effects of the mixtures of chemicals to which humans and wildlife are exposed at once. There is a need for assessment of EDC actions and account the characteristics of the endocrine system, their sensitivity and key variations at different stages of lifecycle. The efficiency of existing testing protocols to identify the effects of exposure to mixture or single EDC inducing combined risks needs to be improved. EDCs are no longer limited to estrogenic, androgenic and thyroid pathways; they also interfere with metabolism, fat storage, bone development and the immune system. New approaches are needed to examine the effects of mixtures of EDCs on disease susceptibility, the etiology and effects that may pass on to upcoming generations. Jayshree *et al.,* 2015.

(2) Improved testing for EDCs: Validated screening and testing systems have been developed by a number of governments, and it requires considerable time and effort to ensure that these systems function properly. These systems include both in vitro and in vivo end-points and various species, including fish, amphibians and mammals to predict toxicity and assess the risk. EDC research over the past decade has revealed the complex interactions of some chemicals with endocrine systems which may escape detection in current validated test systems. Thus, there is a need to uncover the number of chemicals for which there is no information and allow effective consideration of research from all levels — from in vitro mechanistic data to human epidemiological data. Jayshree *et al.,* 2015.

(3) Reducing exposures and thereby vulnerability to disease: It is imperative to know the nature of EDCs to which humans and wildlife are exposed, together with information about their concentrations in the blood, placenta, amniotic fluid and other tissues, across lifespan, sexes, ethnicities (or species of wildlife) and regions. Many information gaps currently exist with regard to what is found in human and wildlife tissues, more so for developing countries, countries with economies in transition and for chemicals that are less bioaccumulative in the body. Biomonitoring of exposures at all critical stages of lifetime such as fetal development, early childhood and the reproductive years is also needed to meet the demand. Since, EDCs are generally present in trace levels and complex matrices, highly selective and sensitive analytical methods are to be developed. Jayshree *et al.,* 2015.

(4) Identifying endocrine active chemicals: Identifying chemicals with endocrine disrupting potential among all of the chemicals used and released worldwide is a major challenge. Though high production volume chemicals could be traced, the complexity increases with the chemicals used as additives and the production of unknown or unintended by-products during chemical manufacturing, combustion processes and via environmental transformations. To know the source of exposure, the active ingredients in pharmaceuticals, pesticides, personal hygiene products and cosmetics where thousands of chemicals are applied, there is a

need to declare the chemical constituents in products, materials and goods (Jayshree *et al*., 2015).

(5) Creating enabling environments for scientific advances, innovation and disease prevention: Exposure to EDCs and their effects on human and wildlife health are a global problem requiring global solutions. More programs are needed that will foster collaboration and data sharing among scientists and between governmental agencies and countries. To protect human health from the combined effects of exposures to EDCs, poor nutrition and poor living conditions, there is a need to develop programs and collaborations among developed and developing countries and those in economic transition. There is also a need to stimulate new adaptive approaches that break down institutional and traditional scientific barriers and stimulate interdisciplinary and multidisciplinary team science (Jayshree *et al*., 2015).

(6) Enhanced methods for evaluating evidence: There is currently no widely agreed system for evaluating the strength of evidence of associations between exposures to chemicals (including EDCs) and adverse health outcomes. A transparent methodology is missing. The need for developing better approaches for evaluating the strength of evidence, together with improved methods of risk assessment, is widely recognized. Methods for synthesizing the science into evidence-based decisions have been developed and validated in clinical arenas. However, due to differences between environmental and clinical health sciences, the evidence base and decision context of these methods are not applicable to exposures to environmental contaminants, including EDCs. To meet this challenge, it is necessary to exploit new methodological approaches (Jayshree *et al*., 2015).

(7) General protective measures to be practiced by people to be protected from endocrine disrupting chemicals are abstaining from heating products wrapped or kept in plastic materials especially in microwave ovens and to prefer ceramic dishes, containers instead of plastics. Furthermore breast milk and baby formulas in plastic bottle should be prevented from contact with microwave. The other measures to be taken for protection from endocrine disrupting chemicals are washing of hands of children for possible contact with pesticides after games, avoiding babies to chew plastic products, not to consume fishes with possible contact with toxic chemicals at most three times a week, to prefer small fishes (Jenkinsa *et at* al., 2012).

Conclusion

The devastating effects of EDCs cannot be over emphasized. In view of current industrialization, there is need to focus future researches on prevention of recirculation of these toxicants as well as improved surveillance and monitoring strategies to detect residues of EDCs in the atmosphere and biosphere. There is need to further elucidate the molecular mechanism by which these EDCs cause toxicity. In addition, application of the above stated control steps will aid in mitigating the effects of EDCs.

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