



Impact of Endocrine Disrupting Chemicals on Human Reproductive System: A Toxicological Perspective

Anu Bela Lakra, Suryapratap Ray and Tejasvi Bhatia†

Department of Forensic Science, Lovely Professional University, Jalandhar-144 411, Punjab, India

†Corresponding author: Tejasvi Bhatia; tejasvi.25999@lpu.co.in

ABSTRACT

Recent clinical or epidemiological studies are reporting alarming results on the effects of certain groups of chemicals on the female reproductive system. These endocrine disrupting chemicals (EDCs) influence the normal activities of hormones secreted from the female hypothalamus, ovary, pituitary & uterus. The female reproductive disorders are mainly observed at embryonic or during fetal development and subsequently get matured during puberty. Various toxic chemicals and other pollutants interact with the chemical structure of the hormones and hence prolonged effects are seen at the cellular and molecular level of hormones resulting in disruption of secretion and function. Due to poor coordination of hormones and other reproductive organs of the body vital functions are compromised. Hence it's highly significant to study and explore the toxicity of chemicals that play a key role in the malfunctioning of the female reproductive system. In this review, we are concerned about the influence of EDCs and their significance in public health. Furthermore, we illustrated the discussion on the increasing effects of EDCs in various parts such as clinical, animal models, or epidemiological studies to develop awareness among the people.

Nat. Env. & Poll. Tech.
Website: www.neptjournal.com

Received: 11-03-2021

Revised: 23-04-2021

Accepted: 02-05-2021

Key Words:

Endocrine disrupting chemicals
Reproductive health
Pralidoxime
Pesticide toxicity

INTRODUCTION

The endocrine system is a part of the organ system that involves chemical messenger as a group of complex networks of the internal gland. It produces, stores, and releases various types of hormones passing through the circulatory system and regulates the target organ and tissue in the body. They perform various functions on the body such as respiration, metabolism, reproduction, sensory perception, movement, sexual development, and growth. Hypothalamus, pituitary, adrenal, penal, ovaries and testes are major hormone producing organs. The chemical structure of hormones can be mainly categorized as proteins & steroids which have functional moiety that interact with various toxic chemicals. These toxic chemicals which are released in the environment may be natural, synthetic, industrial discharge or pesticides. Hence, they can alter the normal hormone function and may cause prolonged effects on living organisms and human health. Such a highly profound class of compounds is known as endocrine disruptor chemicals. An endocrine disrupting chemical (EDC) was defined by the U.S Environment Protection Agency (EPA) as an exogenous agent or mixture that prevent the action of synthesis, secretion, transport, metabolism, binding, action, or elimination of natural Hormone which are responsible for homeostasis, reproduction, and development (Palioura & Diamanti-Kandarakis 2015).

The activity of Endocrine disruptors can be classified as deleterious, pathologic and endocrine mediated disruptions. Since the mid-20th century, numerous studies have reported that Diethylstilbestrol (DES), ethinyl estradiol and synthetic estrogens bind the estrogen receptor and stimulate transcription of estrogen-response genes, which may cause long term effects such as endometriosis, reproductive dysfunction or dysplastic change in humans (Karoutsou et al. 2017). Bisphenol A (BPA) and estrogen receptor (ER) are two contemporary examples of chemicals that have been widely used and have been found in human exposure. Figs. 1, 2 and 3 suggest the chemical structures of some of the PCB and PBBs. Detectable Dioxins, polychlorinated biphenyl (PCBs), polybrominated biphenyl (PBB), polybrominated phenyl ether (PBDE), and insecticides containing halogen groups, among others, imitate natural steroids and serve as antagonists on steroid hormone receptors (Palioura & Diamanti-Kandarakis 2015). Progesterone receptors (PR) are potential targets for many chlorinated EDC such as alkyl-phenols, dichloro- diphenyl- trichloroethane (DDT), and its derivatives (Scippo et al. 2004). Dicarboximide fungicides are major androgen receptors. The important sources of the exposure of EDCs are the food chain, environment, and consumer products. Mostly in human beings and animals, 90% of exposure to EDCs is through contaminants in water, breathing, pollutants in the air, ingesting food, or contam-

inated soil. These environmental toxicants affect human health by absorption, metabolism, accumulation, and interfering through normal functioning and stability. The effect of various toxic chemicals on human health depends on the mechanism of action, solubility in water, the dose-response, and the stability time (Johansson et al. 2021). The steroids and certain groups of pesticides have a large lifetime and hence remain in the environment for a long time.

MECHANISM OF ACTION

Endocrine disruptors affect the endocrine system of humans and animals by mimicking, obstructing, or interfering with the usual plan of action, in which the natural direction of hormones to cells is altered. When EDCs bind to hormone receptors, the transcription of Messenger RNA is altered. This is followed by changes in gene expression, which appears to be one of the most common ways for EDCs to impact endocrine function. The Main nuclear receptors involved in EDCs are ER alpha and beta, AR, thyroid receptors, AhR glucocorticoid receptors (GR) (Bodwell et al. 2004). The progesterone receptor (PR) has recently been highlighted as being more sensitive than the ER-alpha receptor, which has been the target of numerous persistent organic pollutants (POPs) (Villa et al. 2004). Consider the binding/transactivation of Nuclear Receptors in vivo or in vitro models have proved extremely applicable for screening of probable EDCs. Many EDCs do not interact with Nuclear Receptors in any way. Other applicable mechanisms are inhibition of hormone synthesis, transport or metabolism, and activation of Receptors through Receptors phosphorylation or cellular release for hormone action and changes in the hypothalamic-pituitary-gonadal axis. The EDCs mechanisms are depended on Dose-response.

The most disputed issue regarding EDCs is to balance the relationship between dose-response and their mechanism. Because the mimicking or antagonizing activities in normal hormones occur at physiological functional concentrations, the dose-response deliberation for EDCs and other substances working through various routes is less complicated. The estrogenic chemicals produce an inverted U dose-response curve, which can lead to low-dose response activation. Low-dose estrogenic chemicals, such as Bisphenol A and octal phenols, cause deleterious effects. The present criterion Models for assessing modest doses of chemicals that show the form of the dose-response curve are used to undervalue the danger and should be given more consideration (Weltje et al. 2005). Chemicals with distinct mechanisms of action, such as estrogenic, antiandrogenic, growth factor modulation, cytokine and thyroid modulation, and hormone metabolism modulation, have different dose-response curves. Complex mixtures of chemicals have complicated exposure mechanisms; they can affect, but they may not be assigned cautions when compared to single chemicals. EDCs cumulatively, low dose exposure is more potent than high dose exposure, and this shift challenges the traditional toxicological concept. Individual drugs will be studied for probable interactions in the setting of receptor dosage (Koppe et al. 2006). The combined effect of each chemical present at low concentrations was studied (Rasmussen et al. 2003).

When endocrine-disrupting Chemical binds to the specific receptors they inhibit or block or interfere with the mode of action in the endocrine gland. As a result of the buildup of EDCs in the body, gene expression is altered, receptor phosphorylation is altered, and cellular release in the body is altered. The main role of AhR, which are ligand triggered transcription factors, is to regulate the cellular response to-

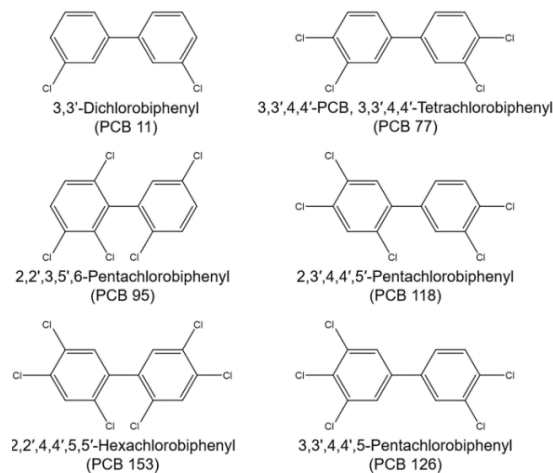


Fig. 1: Chemical Structure of some commonly encountered PCBs.

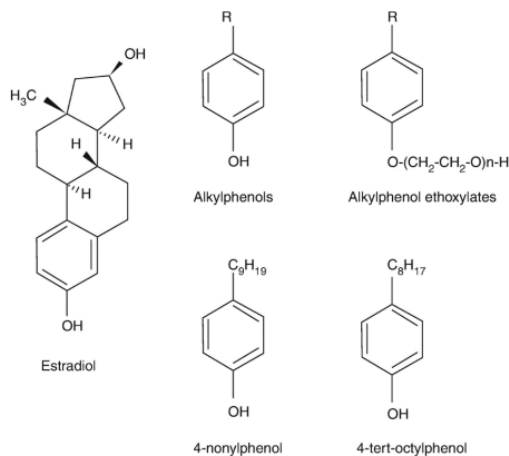


Fig. 2: Structure of some other endocrine disrupting chemicals.

nobiotic exposure. Nuclear receptors are the most commonly targeted receptors by EDCs. These transcription factors are hormone-dependent and may affect the target cells. Many endocrine disrupting drugs (EDCs) have structures that are comparable to NR ligands and can bind to NRs directly. These can either act as agonists and increase gene expression, or they can function as antagonists and block receptor action. EDCs can impact receptor function by promoting receptor degradation, activating the AhR signaling pathway, which will direct the appropriate or common co-activators to the AhR, and interconnect the AhR to bind inhibitory XREs (Swedenborg et al. 2009). Hormone availability is dependent on hormone biosynthesis, transport of the hormone to the target tissue, levels of hormone-binding proteins, and hormone catabolism. EDCs have been described to interfere with all of these processes (Baker et al. 1998; You et al. 2001; Boas et al. 2009). EDCs have a particularly negative impact on steroid hormone catabolism, and many xenobiotic-metabolizing enzymes are implicated in both of these processes. The hydroxylation of 17-estradiol is carried out by the P450 enzymes CYP1A2, CYP3A4, CYP1A1, and CYP1B1, which are all key AhR target genes (Tsuchiya et al. 2005). Upon enzyme activation, xenobiotic exposure causes enhanced hormone catabolism, which compromises hormone signaling. According to a recent experiment, CYP19B (aromatase) is an AhR direct gene that transforms testosterone into estradiol. EDEs prevent AhR activation and increased steroid hormone breakdown, as well as higher estradiol synthesis (Ptak & Gregoraszczyk 2012). Endogenous hormone receptor interferes with endocrine homeostasis. BPA binds with the leptin receptor and it can express itself as ovarian cancer cells and cause ovarian cancer (Ptak & Gregoraszczyk 2012). BPA binds with estrogen and androgen receptors in hypothalamic cells and may cause breast or prostate cancer (Rebuli et al. 2014). Polybrominated diphenyl ethers operate on a hepatic enzyme involved in the glucuronidation pathway, potentially increasing T4 elimination and lowering hormone levels in the blood (Boas et al. 2009). 17 beta-hydroxysteroid hydrogenation binds to parabens. It prevents estrogen dehydration and may even raise hormone levels in the blood (Engeli et al. 2017).

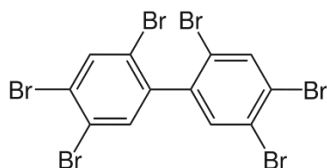


Fig. 3: Structure of polybrominated biphenyl (hexabromobiphenyl).

EDCS RISK ASSESSMENT

Epidemiological studies will discuss the interaction between nutrient toxicants and the new approach will be used in Molecular and epidemiology toxicology, which has been targeted the valuable information about experimental protocol and the mechanistic detection of specific low dose exposure to potential EDCs and has been improved the risk assessment of the adverse health effects of EDCs.

The above-discussed areas such as sources of toxicity, classification, pathways of exposure and mechanism of action have been summarized in Table 1.

EDCS ON FEMALE REPRODUCTIVE HEALTH

Female reproduction and function rely on the coordination of biological processes, which can be disrupted by endogenous or external variables during the developmental stage of life, resulting in negative consequences on female health and reproductive function. The fertility of a woman depends on her reproductive health. Exposure to EDCs, cigarette smoke, and alcohol may exacerbate a woman's fertility problems. Because of lifestyle choices, environmental influences, and older ovulation planning, the female fertility rate has fallen and ovarian disorders such as polycystic ovary syndrome (PCOS), premature ovarian failure (PCF), and primary ovarian insufficiency (POI) have become more common. Bisphenol A (BPA), perfluorooctanoic acid, and perfluorooctane sulfonate are the main causes of these ovarian disorders, according to an epidemiological study. These may disrupt the menstrual cycle's regularities, affecting the quantity and quality of available oocytes, gestational age, weight gain throughout pregnancy, miscarriage risk, and duration of pregnancy in women. This stage begins during embryonic and fetal development and continues through puberty. The interference of EDCs on hormones causes feminine problems in maturity.

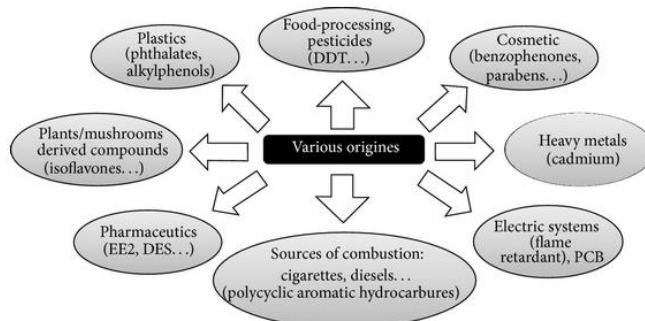


Fig. 4: Sources of EDCs (Kerdivel et al. 2013).

Table 1: Sources of different chemicals, categories, pathways of exposure and mechanism of action.

Chemical(s)	Source	Category	Pathway of exposure	Mechanism of action	Reference
PCBs	Incineration/Landfill	Polychlorinated compounds	Food-chain/living organism	Alteration in steroid hormone/thyroxine transport	(Mantovani et al. 1998, Mantovani 2002)
DDT/DDE/dieldrin	Agriculture run off/atmospheric transport	Organochlorine pesticide	Food-chain/living organisms	Estrogenic activity	(Mantovani et al. 1998, Mantovani 2002)
Triazoles/imidazole			Food-chain/living organism/industrial workplace	Inhibition of steroid hormone biosynthesis	(Mantovani et al. 1998, Mantovani 2002)
Bisphenol A	Consumer products		Food-chain Cosmetics/personal/care/Cleaners/plastics	estrogen agonist-ER alpha (increased ER alpha expression in hypothalamus)	(Scippo et al. 2004)
Parabens	Consumer products		Cosmetics/personal/care/Cleaners/plastics	estrogen agonist-ER alpha and beta	(Oishi et al. 2002, Kunz & Fent 2009)

Fertility and Fecundity

Occupational exposure to insecticides, pesticides, and herbicides plays a significant impact on female fertility and has also been linked to early pregnancy termination and delivery of an immature infant. Direct exposure to these chemicals, primarily through agriculture, has been found in rural women who have worked in the field. In this area, 281 women have been diagnosed with infertility, compared to 216 women who have worked in the agriculture industry. According to this study, women who have been exposed to pesticides for a long time would have an elevated risk of fertility and fecundity (Fuortes et al. 1997) Some males were also exposed to these chemicals, which had negative impacts on their reproductive

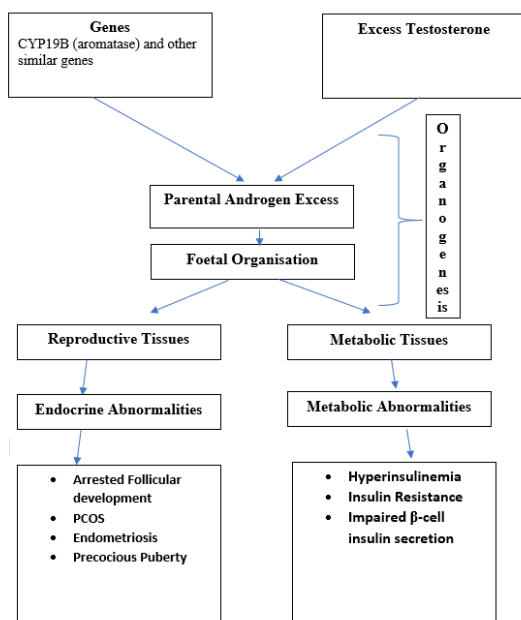


Fig. 5: Diagram illustrating EDCs mechanism of action.

systems. Pesticides such as EDCs, thiocarbamates, atrazine, and phenoxy are to blame, and additional people were exposed through the food chain (Savitz et al. 1997). The chemicals were impurities in water that entered our bodies and disrupted hormone function, resulting in decreased fertility and fecundity in humans and animals.

PCOS (Polycystic Ovarian Syndrome)

PCOS is a heterogeneous syndrome marked by anovulation, oligomenorrhea, and hyperandrogenism in the absence of thyroid, pituitary, or adrenal illness. Insulin resistance is present in PCOS, and the body is unable to utilize insulin effectively as a result of excessive insulin levels in the bloodstream, known as hyperinsulinemia. Increased testosterone levels, as well as obesity and type 2 diabetes, were linked to hyperinsulinemia. Obesity causes a worsening of PCOS by raising insulin levels, which affects the endocrine system and causes problems in the female reproductive system. Obesity and insulin resistance affect roughly half of all women with PCOS, while obese women account for 12% of all PCOS cases (Yildiz et al. 2008). PCOS is a severe illness that affects roughly 6.6 per cent of women in their reproductive years.

Endometriosis

Endometriosis is an estrogen-dependent disease that af-

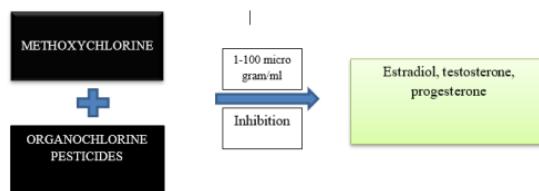


Fig. 6: Inhibition of sex hormones by different pesticides at certain dosages.

fects the endometrial gland and stroma, which are located outside the uterine cavity. It is a prevalent disorder that causes female infertility (Chedid et al. 1995). This condition afflicts approximately 14% of women (Vercillini et al. 1995). While plausible mechanistic hypothesis, the main cause of this condition is influenced by EDCs chemical in estrogen hormone and malfunction the normal function of endometriosis. Endometriosis is caused by chemicals such as polychlorinated biphenyls (PCBs) and TCDD (2, 3,7,8-tetrachlorodibenzo-P-dioxin) (Rier & Foster 2003). These toxic substances alter the menstrual cycle and gonadal steroids and cause female fertility (Yang et al. 2000).

Precocious Puberty

Precocious puberty refers to when a child's puberty begins before the actual age of puberty. It has now become a severe issue in youngsters. The youngsters are affected by pollution and harmful chemicals, which disrupt the hormone function of puberty females and result in negative consequences such as premature breast development or puberty before the age of puberty. Premature breast development in girls and gynecomastia in boys were seen in Puerto Rico in the 1980s. The serum sample was collected from 41 girls. After investigation, it was discovered that 68 per cent of the girls (mean 28 girls) had quantifiable levels of Phthalates (dimethyl, diethyl, dibutyl, and di-(2-ethyl hexyl) in their serum. This toxin is caused by pesticide exposure (root) and induces premature breast development (Colon et al. 2000). The effects of uterine exposure to polybrominated biphenyls (PBS) on sexual maturity were seen in Michigan females whose mothers inadvertently ingested flame retardants as a result of their diet (Blanck et al. 2000).

Uterine Leiomyomas

Smoothing muscle turns into myometrium in the uterus, causing morbidity in women such as menorrhagia, abdominal pain, pelvic prolapse, infertility, and miscarriage. Organochlorine and DES chemicals generated uterine Leiomyomas by causing germ-line mutation. (Buttram et al. 1981).

Breast and Endometrial Cancer

Menarche, first pregnancy, menopause, lactation, and parity are all risk factors for breast cancer. All of these parameters are linked to ovarian hormone exposure throughout time.

Breast cancer

Breast cancer risk is influenced by dietary variables. Dietary substances that are phytoestrogens (soy products) have been linked to a decrease in steroid hormone levels due to the direct regulation of 17 beta - E2 biosynthesis and metabolism (Lim-

er & Speirs 2004). DDT metabolism has been discovered in human serum, adipose tissue, and breast milk. There is an increased risk of estrogen-dependent malignancies like breast cancer as a result of occupational exposure through food. The link between polychlorinated biphenyl (PCB) exposure and breast cancer is occupational, although there is no evidence of a positive effect. According to recent research, underarm cosmetics may contribute to the development and progression of breast cancer. A range of endocrine active substances (e.g., parabens) is used in cosmetics and are typically used in the area directly adjacent to the breast (Darbre 2006).

Endometrial Cancer

After 5 years of treatment with 50 mg of soy isoflavones, a study of 298 postmenopausal women found an elevated risk of endometrial hypoplasia (Unfer et al. 2004). Phytoestrogen is being re-evaluated as a high-risk factor for endometrial cancer in women. Diethylstilbestrol (DES) exposure increased the incidence of a host, altered the ovary and reproductive tract, and caused the ovarian effect, reproductive abnormalities in women, such as vaginal adenosis, cervical and vaginal hypoplasia, uterine and tubal abnormalities, infertility, early menopause, and breast cancer. The spectrum of possibilities is demonstrated by changes in the developing ovary with or without changes in hormonal signaling.

EDCS ON MALE REPRODUCTIVE HEALTH

The endocrine system's function was affected by environmental pollutants. Epidemiological research is being used to better understand the impact of EDCs on human reproductive development and function. This research examined the failure of normal hormone activity and how it affected male reproductive health, among other things. Changed fetal development, manifested as urogenital tract anomalies, and disrupted reproduction function, manifested as lower semen quality and sterility (Hypospadias, Cryptorchidism) Germ cell cancer of the testes (TGCC).

Hypospadias

The effect of hypospadias was increased by 0.4 per cent when the meatus was on the central side of the penis at the time of birth (Nassar et al. 2007). VCZ (vinclozolin) and phthalates are two factors that contribute to EDCs (Schneider et al. 2011, Mylchurst et al. 2000).

Cryptorchidism

Failure of one or both testicles, resulting in abnormalities in the scrotal sac, is a 2-4 per cent common congenital condition affecting male children (Boisen et al. 2004). Adulthood is an

Table 2 : Targeted organs and resulting diseases by different groups of pesticides.

Pesticides Category	Targeted organ(s)/function	Diseases
Organochlorine DDT/DDE Aldrin and Dieldrin	Acetylcholinesterase inhibitors / Liver	Metabolic syndrome (diabetes and obesity), precocious puberty, breast cancer, reduced semen quality disrupted mensuration, lactation problem
Organophosphate Malathion and parathion Chlorpyrifos	Acetylcholinesterase inhibitors /cardiovascular system, nervous system, respiratory	Breast cancer Developmental delays, attention problems, ADHD in children
Methyl parathion, Ronnel, Dione fox		Endometriosis, prostate cancer
Carbamates Carbofuran	Acetylcholinesterase inhibitors/central nervous system, nicotinic receptor in skeletal muscle tissue	Autoimmune disease
Pyrethroids Deltamethrin	Act on the neural dopamine transport/alter the function of the central nervous system	Parkinson disease Sleep disorder, impaired memory

unfavorable risk factor for infertility and testicular cancer (Foresta et al. 2007). Leydig cells exposed to ED (Endocrine disruptors) at both stages were lowering insulin-like 3 factors (Emmen et al. 2000) and impairing steroidogenesis (related to testosterone deficiency), PBDE exposure through nursing has been linked to cryptorchidism in newborns (Main et al. 2007).

Testicular Dysgenesis Syndrome

A Unifying Theorem: - The Hypothesis will reduce TGCC and male urogenital tract abnormalities, which are two typical pathways for sperm quality. EDCs, environmental chemicals, and genetic variables all interact through a similar pathway to produce anomalies in fetal testis development, resulting in Testicular Dysgenesis (Skakkebaek et al. 2001). All of these disorders show a higher incidence of urogenital anomalies in newborn males, as well as impaired semen quality and TGCC in young men. TDS (Testicular Dysgenesis Syndrome) is caused by a combination of parental Leydig cell failure and sertoli cell dysfunction, as well as secondary androgen and poor germ cell development. (Słowikowska-Hilczer et al. 2001). Semen quality, TGCC, and urogenital abnormalities are caused by chemicals such as PCBs, pesticides (persistent or non-persistent), and phthalates. There was no link between TCDD and sperm quality in men aged 18 to 26. Men who were exposed between the ages of 1 and 9 and between the ages of 10 and 17 had lower estradiol and higher FSH concentration than men who were not exposed (Evanthia et al. 2009). These findings show that the timing of exposure,

or life stage, may play a role in determining the impact of environmental exposure (Roberts et al. 2005).

Pesticides are a large group of heterogeneous chemicals that may cover various products such as insecticide, herbicides fungicides, and rodenticide. Acetylcholinesterase inhibitors include organochlorine, organophosphate, and carbamates. In cases of accidental or deliberate drunkenness, this is a common occurrence. Carbamates and organochlorine insecticides cause fatal poisoning, but herbicides, chlorophenoxyacetic acid, and some pyrethroids cause less poisoning (Goel & Aggarwal 2007, Singh & Sharma 2000). Different classes of pesticides act on different sites and may cause various diseases. Table 2 below illustrates the summary of such activities. The first symptoms in the muscarinic and central nervous systems develop within 1-2 hours of organophosphate exposure. Salvation, lacrimation, urine, feces, gastrointestinal cramps, and emesis are all symptoms of muscarinic toxicity. SLUDED was used to represent all of these qualities, and DUMBLES was used for other acronyms (diarrhea, urination, miosis, bronchorrhoea, emesis, and sweating) (Sivagnanam 2002, Karatas et al. 2006). Headache, tremors, restlessness, ataxia, weakness, emotional lability, disorientation, slurring, coma, and seizure are all neurological clinical characteristics. The first signs of organochlorine poisoning are nausea, vomiting, dizziness, convulsions, confusion, or coma, which appear within 30 minutes of exposure (Karatas et al. 2006). The impact on the presynaptic and postsynaptic junction is the acute poisoning syndrome of organophosphate related to toxic-induced my-

opathy (Singh & Sharma 2000). After 1-4 days of exposure to OP, neuropathic targets are inhibited, and the respiratory system fails or weakens (Singh & Sharma 2000). After 10-20 days, the delayed effect caused a neuropathy known as ginger paralysis syndrome (Ladell 1961). Table 2 represents the classification of pesticides while suggesting the targeted organs and the resulting diseases (Balali-Mood & Shariat 1998, Ladell 1961).

The activity of Butyrylcholinesterase, plasma cholinesterase, and red cell cholinesterase can be used to make a diagnosis. The typical exposure of red cell cholinesterase is roughly 30-50 per cent; this will be lowered to 20%. Pseudocholinesterase activity can be used to identify intoxicating drugs at low concentrations (morphine or codeine), which can induce chronic liver disease, pregnancy, neoplasm, infection, and malnutrition, but it is also unreliable due to these circumstances. Diazinon has a greater effect on plasma cholinesterase than on red cell acetylcholinesterase (Eddleston et al. 2002).

For monitoring the seizure, we use the ABC (absorption, breathing, and circulation) method to avoid toxin absorption, and then we use various medications such as Epinephrine and cholestyramine for further therapy. Patients' heart rates can be controlled using dopamine. In some cases, cholestyramine resin is utilized for fecal excretion in Organochlorine compounds at a dose of 4 g four times a day. In the event of myocardial infarction, epinephrine should be avoided (Cohn et al. 1978). When first exposed to OP, we shall use the ABC approach, i.e. (Airways, Breathing, Circulation, Distribution). For toxic patients, early oxygen treatment is critical. During oxygen treatment, the patient's head is normally put on the lower side and the abdomen region is placed on the left side. Atropine and pralidoxime (PAM/2-pyridine aldoxime Methyl chloride) are two medications that are used for therapy (Sivakumar et al. 2006). Atropine medications, which are used to treat hypothermic patients but are preferable to Diazepam, will be avoided in Haloperidol for sedation since they are pro-convulsant and will disrupt the central thermoregulation of the QT interval. (Balali & Shariat 1998, Roberts & Buckley 2005). PAM can be used in various anticholinesterase functions (Eddleston et al. 2002). PAM will be avoided in case of carbamate poisoning because of the short period of action of carbamates (Goel et al. 2007).

Pralidoxime and Carbamate Toxicity

Pralidoxime or (2- PAM) at carbamates toxicity cannot be engaged due to the following reason. Carbamate reversibly binds to Acetylcholinesterase (Eddleston et al. 2002). Carbamate such as carbaryl has shown poor outcomes when treated with pralidoxime. They activate the cholinesterase

inhibitor (such as neostigmine and pyridostigmine) at the absorption or redistribution process (Ekins & Geller 1994). Carbamate is avoided at "aging" because they occur during the phosphorylation of organophosphate to acetylcholinesterase. Carbamate-cholinesterase bond does not hydrolyze at aging because this does not have phosphate groups. 2-PAM mostly affects nicotinic receptors as well as Muscarinic receptors because 2-PAM is a quaternary nitrogen compound and cannot cross the blood-brain barriers (BBB). When 2-Pam will be administrated that will be disbalancing the CNS system and the patient can be in a coma (Kurtz 1990).

CONCLUSION

It is clear from the above discussion that the extensive bioavailability of EDCs in the environment causes various health issues in humans. For such toxic elements, various animals including other ecosystems are getting affected as well. The disturbances in the food chain due to the fluctuation in ecosystem health are a threat to earth. Awareness among people can reduce toxicity which can help recreate a healthy atmosphere. However, different toxicities are already mentioned in the above discussion. The toxicological assessment was done including the diagnosis, treatment, etc. Pralidoxime is not being used in carbamate intoxication treatment. Atropine and the PAM can be used in other pesticide intoxication treatments though. The reduction in the use of various synthetic chemicals for various purposes must be done earlier to reform our ecosystems, which can ultimately provide improved public health.

REFERENCES

- Arbuckle, T. E., Savitz, D. A., Mery, L. S. and Curtis, K. M. 1999. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology* (Cambridge, Mass.), 10(6): 752-760. doi:10.1097/00001648-199911000-00017
- Baker, M. E., Medlock, K. L. and Sheehan, D. M. 1998. Flavonoids inhibit estrogen binding to rat alpha-fetoprotein. *Proceedings of the Society for Experimental Biology and Medicine*. Society for Experimental Biology and Medicine (New York, N.Y.), 217(3): 317-321. doi:10.3181/00379727-217-44238
- Balali-Mood, M. and Shariat, M. 1998. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *J. Physiol.*, 92(5-6): 375-378.
- Blanck, H.M., Marcus, M., Tolbert, B.E., Rubin, C., Henderson, A.K., Vs, H. and Cameron, L. 2000. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology*, 11: 641-647.
- Boas, M., Main, K. M. and Feldt-Rasmussen, U. 2009. Environmental chemicals and thyroid function: an update. *Current Opinion in Endocrinology, Diabetes, and Obesity*, 16(5): 385-391. doi:10.1097/MED.0b013e3283305af7
- Bodwell, J.E., La, K. and Hamilton, J.W. 2004. Arsenic at very low concentration alters glucocorticoid receptor (GR) – Mediated gene activation but not GR- mediated gene repression: Complex dose-response effects

- are closely correlated with the level of activated GR and required a functional GR DNA binding domain. *Chem. Res. Toxicol.*, 17: 1064-1076.
- Boisen, K.A., Kaleva, M., Main, K.M., Virtanen, H.E., Haavisto, A.M., Schmidt, I. M. and Reunanen, M. 2004. The difference in the prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet*, 363: 1264-1269.
- Buttram, V. C., Jr. and Reiter, R. C. 1981. Uterine leiomyomata: Etiology, symptomatology, and management. *Fertility and Sterility*, 36(4): 433-445. doi:10.1016/s0015-0282(16)45789-4
- Chedd, S., Camus, M., Smitz, J., Van Steirteghem, A. C. and Devroey, P. 1995. Comparison among different ovarian stimulation regimens for assisted procreation procedures in patients with endometriosis. *Human Reproduction (Oxford, England)*, 10(9): 2406-2411. doi:10.1093/oxfordjournals.humrep.a136308.
- Cohn, W. J., Boylan, J. J., Blanke, R. V., Fariss, M. W., Howell, G. and P S. 1978. Treatment of chlordecone (Kepone) toxicity with cholestyramine: Results of a controlled clinical trial. *N. Engl. J. Med.*, 298: 243-8.
- Colon, I., Caro, D., Bourdony, C.J. and Rosario, O. 2000. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ. Health Persp.*, 108(9): 895-900.
- Darbre, P.D. 2006. Environmental estrogens, cosmetics, and breast cancer: Best practice & research. *Clinical Endocrinol. Metabol.*, 20(1): 121-143.
- Eddleston, M., Szinicz, L., Eyer, P. and Buckley, N. 2002. Oximes in acute organophosphorus pesticide poisoning: A systematic review of clinical trials. *QJM*, 95(275-83): 24.
- Ekins, B.R. and Geller, R.J. 1994. Methomyl-induced carbamate poisoning treated with pralidoxime chloride. *Western J. Med.*, 161(1): 68-70.
- Emmen, J.M., McLuskey, A., Adham, I.M., Engel, W., Verhoef-Post, M., Themmen, A.P. and Brinkmann, A.O. 2000. Involvement of insulin-like factor 3 (InsI3) in diethylstilbestrol-induced cryptorchidism. *Endocrinology*, 141: 846-849.
- Engeli, R.T., Rohrer, S.R., Vuorinen, A., Herdinger, S., Kaserer, T., Leugger, S., Schuster, D. and Odermatt, A. 2017. Interference of paraben compounds with estrogen metabolism by inhibition of 17 -hydroxysteroid dehydrogenases. *International journal of molecular sciences*, 18(9): 2007.
- Foresta, C., Zuccarello, D., Garolla, A. and Ferlin, A. 2008. Role of hormones, genes, and environment in human cryptorchidism. *Endoc. Rev.*, 29(5): 560-580.
- Fuortes, L., Clark, M. K., Kirchner, H. L. and Smith, E. M. 1997. Association between female infertility and agricultural work history. *American Journal of Industrial Medicine*, 31(4): 445-451.
- Goel, A., Aggarwal, P., Bhoi, S. and Gupta, V. 2007. High-dose pralidoxime for organophosphorus poisoning. *Lancet*, 369(9571): 1425. doi:10.1016/s0140-6736(07)60657-6
- Johansson, H. K. L., Christiansen, S., Draskau, M. K., Svingen, T. and Boberg, J. 2021. Classical toxicity endpoints in female rats are insensitive to the human endocrine disruptors diethylstilbestrol and ketoconazole. *Reproductive Toxicology (Elmsford, N.Y.)*, 101: 9-17. doi:10.1016/j.reprotox.2021.01.003
- Karatas, A.D., Aygun, D. and Baydin, A. 2006. Characteristics of endosulfan poisoning: A study of 23 cases. *Sing. Med. J.*, 47(12): 1030-1032.
- Karoutsou, E., Karoutsos, P. and Karoutsos, D. 2017. Endocrine disruptors and carcinogenesis. *Archives in Cancer Research*, 05(01) doi:10.21767/2254-6081.1000131
- Kerdivel, G., Habauzit, D. and Pakdel, F. 2013. Assessment and molecular actions of endocrine-disrupting chemicals that interfere with estrogen receptor pathways. *International Journal of Endocrinology*. doi:10.1155/2013/501851
- Koppe, J.G., Bartonova, A., Bolte, G., Bistrup, M.L., Busby, C., Butter, M. and Zuurbier, M. 2006. Exposure to multiple environmental agents and their effect. *Acta Paed.*, 95(453): 106-113.
- Kunz, P.Y. and Fent, K. 2009. Estrogenic activity of ternary UV filter mixtures in fish (*Pimephales promelas*): An analysis with nonlinear isobolograms. *Toxicol. Appl. Pharmacol.*, 234(1): 77-88.
- Kurtz, P.H. 1990. Pralidoxime in the treatment of carbamate intoxication. *The Amer. J. Emergency Med.*, 8(1): 68-70.
- Ladell, W.S. 1961. Physiological and clinical effects of organophosphorus compounds. *J. R. Soc. Med.*, 54(5): 405-406.
- Limer, J.L. and Speirs, V. 2004. Phyto-oestrogens and breast cancer chemoprevention. *Breast Cancer Res.*, 6: 119-127.
- Main, K.M., Kiviranta, H., Virtanen, H.E., Sundqvist, E., Tuomisto, J.T., Tuomisto, J. and Toppari, J. 2007. Flame retardants in the placenta and breast milk and cryptorchidism in newborn boys. *Environ. Health Persp.*, 115(10): 1519-1526.
- Mantovani, A. 2002. Hazard identification and risk assessment of endocrine-disrupting chemicals with regard to developmental effects. *Toxicology*, 181-182, 367-370.
- Mantovani, A., Stazi, A.V., Macrì, C., Maranghi, F. and Ricciardi, C. 1998. Problems in testing and risk assessment of endocrine-disrupting chemicals with regard to developmental toxicology. *Chemosphere*, 39(8): 1293-1300.
- Mylchrest, E., Wallace, D.G., Cattley, R.C. and Foster, P.M. 2000. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. *Toxicol. Sci.*, 55: 143-151.
- Nassar, N., Bower, C. and Barker, A. 2007. Increasing Prevalence of Hypospadias in Western Australia, 1980-2000.
- Palioura, E. and Diamanti-Kandarakis, E. 2015. Polycystic ovary syndrome (PCOS) and endocrine disrupting chemicals (EDCs). *Reviews in Endocrine & Metabolic Disorders*, 16(4): 365-371. doi:10.1007/s11154-016-9326-7
- Ptak, A. and Gregoraszczuk, E.L. 2012. Bisphenol A induces leptin receptor expression, creating more binding sites for leptin, and activates the JAK/Stat, MAPK/ERK and PI3K/Akt signalling pathways in human ovarian cancer cell. *Toxicology Letters*, 210(3): 332-337.
- Rasmussen, T.H., Nielsen, F., Andersen, H.R., Nielsen, J.B., Weihe, P. and Grandjean, P. 2003. Assessment of xenoestrogenic exposure by a biomarker approach: application of the E-Screen bioassay to determine the estrogenic response of serum extracts. *Environ. Health - Global Access Sci. Source*, 2(1): 12.
- Rebuli, M.E., Cao, J., Sluzas, E., Delclos, K.B., Camacho, L., Lewis, S.M., Vanlandingham, M.M. and Patisaul, H.B. 2014. Investigation of the effects of subchronic low dose oral exposure to bisphenol A (BPA) and ethinyl estradiol (EE) on estrogen receptor expression in the juvenile and adult female rat hypothalamus. *Toxicological Sciences*, 140(1): 190-203.
- Rier, S. and Foster, W.G. 2003. Environmental dioxins and endometriosis. *Seminars in Reprod. Med.*, 21(2): 145-154.
- Roberts, D. and Buckley, N.A. 2005. Alkalinisation for organophosphorus pesticide poisoning. *Cochrane Database System. Rev.*, (1): CD004897.
- Roberts, D. M., Fraser, J. F., Buckley, N. A. and Venkatesh, B. 2005. Experiences of anticholinesterase pesticide poisonings in an Australian tertiary hospital. *Anaesthesia and Intensive Care*, 33(4): 469-476. doi:10.1177/0310057X0503300408.
- Savitz, D.A., Arbuckle, T., Kaczor, D. and Curtis, K.M. 1997. Male pesticide exposure and pregnancy outcome. *Amer. J. Epidemiol.*, 146(12): 1025-1036.
- Schneider, S., Kaufmann, W., Strauss, V. and Ravenzwaay, B. 2011. Vinclozolin: a feasibility and sensitivity study of the ILSI-HESI F1-extended one-generation rat reproduction protocol. *Regul. Toxicol. Pharmacol.*, 59: 91-100.
- Scippo, M.L., Argiris, C., Van De Weerd, C., Muller, M., Willemsen, P., Martial, J. and Maghuin-Rogister, G. 2004. Recombinant human estrogen, androgen, and progesterone receptors for detection of potential endocrine disruptors. *Anal. Bioanal. Chem.*, 378(3): 664-669.

- Sivakumar, S., Raghavan, K., Ishaq, R. M. and Geetha, S. 2006. Organophosphorus poisoning: A study on the effectiveness of therapy with oximes. *J. Assoc. Physicians*, 54(250): 1.
- Singh, S. and Sharma, N. 2000. Neurological syndromes following organophosphate poisoning. *Neurol. India*, 48(4): 308-313.
- Sivagnanam, S. 2002. Potential therapeutic agents in the management of organophosphorus poisoning. *Critical Care*, 6(3): 260-261.
- Skakkebaek, N.-E., Meyts, E. R. and Main, K. M. 2001. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *APMIS: Acta Pathologica, Microbiologica, et Immunologica Scandinavica*, 109(S103): S22-S30. doi:10.1111/j.1600-0463.2001.tb05770.x
- Slowikowska-Hilczer, J., Szarras-Czapnik, M. and Kula, K. 2001. Testicular Pathology in 46, XY genetic male pseudohermaphroditism: an approach to the pathogenesis of testis cancer. *J. Androl.*, 22: 781-792.
- Swedenborg, E., Rüegg, J., Mäkelä, S. and Pongratz, I. 2009. Endocrine disruptive chemicals: mechanisms of action and involvement in metabolic disorders. *Journal of Molecular Endocrinology*, 43(1): 1-10. doi:10.1677/JME-08-0132.
- Tsuchiya, Y., Nakajima, M. and Yokoi, T. 2005. Cytochrome P450-mediated metabolism of estrogens and its regulation in humans. *Cancer Letters*, 227(2): 115-124. doi:10.1016/j.canlet.2004.10.007
- Unfer, V., Casini, M. L., Costabile, L., Mignosa, M., Gerli, S. and Di Renzo, G. C. 2004. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fertility and Sterility*, 82(1): 145-148. doi:10.1016/j.fertnstert.2003.11.041
- Vercillini, P., Oldani, S., De Giorgi, O., Coutinho, C. P. G., Em, S. and P, de Moura. (1995). *Endometriosis: An Overview of Descriptive and Analytic Epidemiological Studies, Progress in the Management Of Endometriosis*. New York Parthenon Publishing Group.
- Villa, R., Bonetti, E., Penza, M.L., Lacobello, C., Bugari, G., Bailo, M. and Ciana, P. 2004. Target-specific action of an organochlorine compound in reproduction and non-reproduction tissue of estrogen-reporter male mice. *Toxicol. Appl. Pharmacol.*, 201: 137-148.
- Weltje, L., Vom Saal, F.S. and Oehlmann, J. 2005. Reproductive stimulation by the low dose of xenoestrogens contrasts with the view of hormesis as an adaptative response. *Hum. Exp. Toxicol.*, 24: 431-437.
- Yang, J.Z., Agarwal, S.K. and Foster, W.G. 2000. Subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin modulates the pathophysiology of endometriosis in the cynomolgus monkey. *Toxicol. Sci.: J. Society Toxicol.*, 56(2): 374-381.
- Yildiz, B. O., Knochenhauer, E. S. and Azziz, R. 2008. Impact of obesity on the risk for polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*, 93(1): 162-168. doi:10.1210/jc.2007-1834
- You, L., Sar, M., Bartolucci, E., Ploch, S. and Whitt, M. 2001. Induction of hepatic aromatase by p,p'-DDE in adult male rats. *Molecular and Cellular Endocrinology*, 178(1-2): 207-214. doi:10.1016/s0303-7207(01)00445-2