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CHEMICAL NATURE, MECHANISMS AND GENERAL CHARACTERISTICS OF ENDOCRINE DISRUPTORS. AN OVERVIEW

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ABSTRACT

There has been an increase in human studies of exposure to endocrine-disrupting chemicals (EDCs). In this follow-up to a previous study, we analyzed new data to determine whether or not there was substantial human evidence linking the exposures and outcomes of the prior study. Perfluoroalkyl chemicals have been linked to an increased risk of childhood and adult obesity, impaired glucose tolerance, gestational diabetes, low birth weight, poor sperm quality, polycystic ovary syndrome, endometriosis, and breast cancer. There is substantial evidence supporting these associations. Children exposed prenatally to bisphenol A, organophosphate insecticides, and polybrominated flame retardants are more likely to develop cognitive impairments and attention-deficit hyperactivity disorder. Although a comprehensive evaluation of the frequency and intensity of these exposure-result links is required, a growing body of evidence suggests that immediate action be taken to reduce exposure to environmental toxicants (EDCs).

Our environment has become contaminated enormously with different industrial chemicals that could disturb the natural mechanism of hormones like their secretion, transport etc., in our body. These industrial effluents are called as endocrine disruptors (EDs) and they mainly affect through polluted water and food. These chemicals (EDs) have the ability to stay in the environment for years and to travel vast distances due to their long half-life. Plastics, fungicides, pesticides, medications, plasticizers, lubricants, and so on are only few examples of the wide range of potential environmental contaminants (EDs). Due to the complexity of the situation, it is difficult to understand the precise mechanism of action of these EDs, which cause disruptions in hormone production or epigenetic pathways as well as in thyroid receptors (TRs), oestrogen receptors (ER), androgen receptors (AR) and aryl hydrocarbon receptors (AhR). The research advancements in

this area is mandatory to get more information about EDs, their potential and their mode of action and removal of these chemicals from environment.

Keywords: Endocrine Disrupting Chemicals EDCs, toxicity mechanism, mixture interaction.

INTRODUCTION

In 1962, Rachel Carson warned about DDT's negative effects on sexual development and reproduction [1]. A cluster of vaginal cancer cases was reported by Herbst and colleagues in Boston (MA, USA) less than 10 years later, and they related it to prenatal dosage with the medication diethylstilbestrol. It was often held at the time that synthetic chemicals could only rarely alter hormonal and homoeostatic processes, and so contribute to disease and dysfunction [2]. This idea was similar to the Paracelsian concept that "Solely the dose determines that a thing is not a poison."

In the last fifty years, these two assumptions have been thoroughly debunked. Several studies have shown that various exogenous chemicals affect endocrine processes and functions, highlighting the urgent need for a new scientific paradigm. Numerous studies have shown evidence for dose-response correlations that are not monotonic [3]. Mechanistic studies have provided a molecular level explanation for these seemingly random combinations. These EDCs are not random pharmacy mistakes or accidental spills. The FDA has identified more than 1800 chemicals as potential disruptors of the oestrogen, androgen, or thyroid endocrine pathways. There were 575 chemicals tested after a request from the European Commission, and 4,320 of them showed signs of endocrine disruption. A rising body of evidence suggests that five EDCs pose particularly severe and urgent threats to human health and may soon rank among the world's most pressing environmental issues. Many groups are keeping track of the mounting evidence and its implications for human health, including the Endocrine Society, the International Federation of Gynecology and Obstetrics, the World Health Organization, the United Nations Environment Programmed, the American Academy of Pediatrics, and many more [4]. They describe the severe adverse effects of EDCs on endocrine processes during vulnerable periods of human development and the long latency period between exposure and disease, and they link early life exposure to chemicals like DDT to the incidence of breast cancer half a century later [5].

This paper aims to add to the previous report by identifying new exposure-outcome associations of concern, particularly in regards to chemicals that were not widely researched a few years ago, such as perfluoroalkyl and polyfluoroalkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs), and by including several outcomes that were not specifically focused on in the WHO and UNEP report, such as anogenital distance and prostate cancer. To further inform future research and policy, we have focused on currently circulating synthetic chemicals rather than legacy molecules like DDT and other organochlorine pesticides, polychlorinated biphenyls (PCBs), and dioxins and furans. When possible, we emphasize studies that show alternatives to banned or phased-out drugs work just as well, if not better.

Evidence suggests that male fertility is declining across a wide range of species, including humans and animals. The quantity of man-made chemicals utilized and released into the environment has increased steadily over the last half-century. It was subsequently shown that certain chemicals may interfere with the proper development of the endocrine system in the developing embryos of experimental animals. Male progeny exposed to the therapy had fertility problems that were consistent with those seen in humans and other mammals. In addition, both human DES and rodent studies have shown windows of opportunity during pregnancy when the developing fetal gonad is most vulnerable to even small alterations in endocrine function. Genes susceptible to EDCs have been successfully identified in both in vivo animal studies and in vitro human studies. This has led to the formation of hypotheses concerning the underlying mechanism of action. Disrupted testicular apoptosis and altered steroid biotransformation in the liver are two such possibilities. However, it is challenging to link the results of animal research to the findings of human studies due to the fact that different study groups utilize varying maternal doses. However, there are important insights that can be gleaned from animal research regarding the range of outcomes that may be connected to in utero EDC exposure. The normal prenatal exposure dosage of EDC is still unknown. Because of (a) the large number of chemicals that are considered EDCs, (b) the ability of chemicals to bioaccumulate in body lipid, (c) the metabolism of body lipid during pregnancy, which releases the mother's lifetime EDC legacy into circulation, and (d) the poorly understood kinetics of EDC transfer across the placenta, the issue is complicated. Consequently, the extent to which the fetus was exposed can only be estimated at this time. Because of this, studies examining

the movement of EDCs through the placenta and the distribution of EDCs between the mother and the baby using large animal models are urgently needed. Although a lot of effort has gone into studying the effects of endocrine disrupting chemicals, the mechanisms by which they function remain mostly unknown. More investigation into the mechanism of action and the effects of EDCs on fetal development is needed to better understand how these chemicals exert their effects. This will help us learn more about the power and effect of EDCs. Only a combined approach combining in vitro human research with animal models will allow for this to be achieved. Overall, the present body of data from animal models suggests that EDCs may have an adverse effect on male reproductive development and function. With further insight into the underlying causes, we can work toward designing intervention strategies that will hopefully reverse the declining state of men's and women's reproductive health [6].

The sections that follow describe the evidence linking EDCs to adverse perinatal, neurodevelopmental, metabolic, and reproductive effects, many of which were previously recognized or are becoming increasingly plausible. In the appendix, you will find nuanced findings and tables that summarize all the research we reviewed that indicated statistically or epidemiologically significant associations. Finally, we summarize the remaining information gaps and potential avenues for future human research to complete them.

CHARACTERISTICS OF ENDOCRINE DISRUPTORS (EDs)

Plastics, detergents, pesticides, and cosmetics are just some of the many industrial chemicals that have contaminated the environment since the middle of the 20th century. Contaminants in the environment may harm an organism or its progeny by interfering with the normal functioning of the homeostatic and hormonal feedback loops. As a result, these substances have been dubbed endocrine disruptors (EDs) in the industrial chemical community [7]. Hormone synthesis, secretion, transport, removal, and binding may all be affected by environmental drift agents (EDs). In this case, the EPA is the source of the definition. Hormone disruption disrupts the body's equilibrium and the regulation of development, behavior and reproduction [8]. Contaminated soil, air, water or food may introduce EDs into the bodies of people and other animals [9]. EDs affect hormone expression, activity and production at the receptor target by changing, imitating or

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antagonizing the levels of endogenous steroid. There are some properties of EDs that can increase their hazardous effects. Adipose tissue is a common storage site since many of these chemicals are lipophilic [10]. Several studies have indicated that the effects of EDs are enhanced when taken in combination, and the NOEL for EDs alone is low.

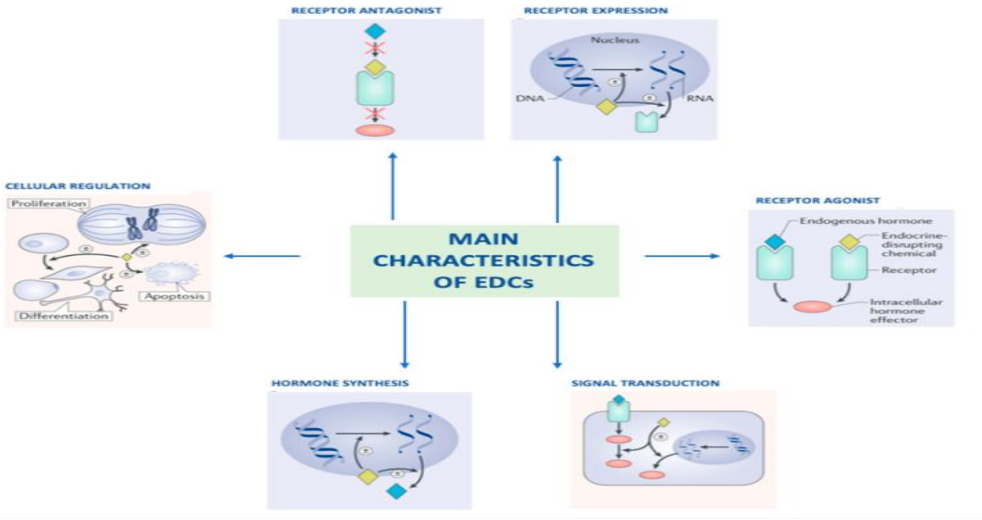

Fig 1. Main characteristics of EDCs

However, it has been proven that mixtures including EDs have detrimental effects [11], thus we should redirect our focus to studies of mixtures containing these chemicals. The non-linear dosage response effect is the most common adverse effect of EDs [12], in which low dosages cause more expansive responses than high doses. Furthermore, EDs show varying responses across the lifespan in line with physiological amounts of hormones. Risk assessment techniques that don't take into consideration developmental milestones [13, 14] have trouble accounting for these variations in responses. When employing parent medicines, many in vitro studies neglect to include EDs.

AN ENDOCRINE DISRUPTOR'S CHEMICAL MAKEUP

The diverse collection of known EDs may be broken down into two distinct categories: 1) The first kind is produced in a laboratory setting. They are categorized as i) Industrial, solvents and their byproducts. Some examples of these byproducts are polychlorinated biphenyls (PCBs), dioxins and polybrominated diphenyl ethers (PBDE). Other examples include 2,3,7,8-

tetrachlorodibenzo-p-dioxin (TCDD) and decabromodiphenylethane (DBPDE). ii) Bisphenols that are found in plastics, such as bisphenol A (BPA) and bisphenol S (BPS). iii) Pesticides, such as methoxychlor (MTX), cypermethrin, dichlorodiphenyltrichloroethane (DDT), atrazine as well as the pesticide's metabolites, such as 2,2-bis(p-hydroxyphenyl) and endosulphan; and iv) Herbicides, such as thiamethoxam and chlorpyrifos; and v) plasticizers; for example, phthalates;1,1,1-trichloroethane, often known as HPTE, vi) fungicides; for example, vinclozolin (VCZ), hexachlorbenzene (HCB) dicarboximid; vii) medicines; for example, non-steroidal anti-inflammatory medications (NSAID), acetaminophen, diethylstilbestrol (DES) and ethinyloestradiol (EE),. 2) The second category of EDs are those that are produced naturally, such as natural chemicals such as genistein and phytoestrogens.

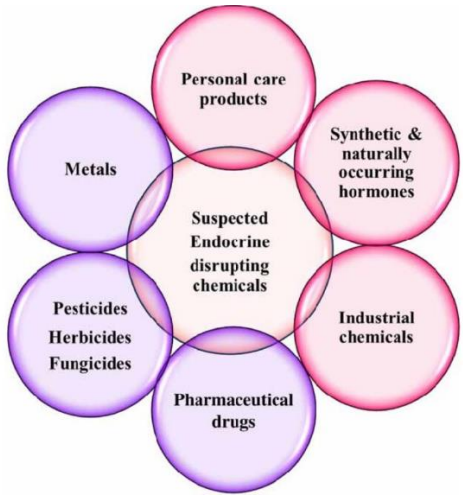

Fig. 2 Suspected Endocrine Disrupting Chemicals

MECHANISMS OF EDs

Because of the complexity of the endocrine system, it is not possible to grasp the mechanism of EDs in its whole [16]. They exert their effect by interfering with many receptors, including the the thyroid receptors (TRs), androgen receptor (AR), the progesterone receptors, and the oestrogen receptors (ER) [2]. The body is duped into believing that EDCs are hormones via the "lock and key" concept, which depicts how EDCs work.

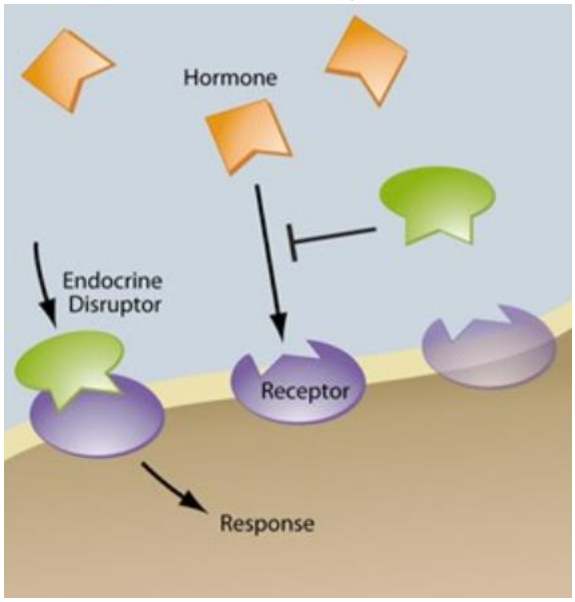

Fig 3. Mechanistic step of EDCs

EDCs EFFECTS ON THYROID, ESTROGEN AND ANDROGEN RECEPTORS

When endogenous depressants attach to receptors, they might set off two distinct kinds of reactions. The first is a positive hormonal reaction, which has an agonistic impact, and the second is a negative hormonal response, which has an antagonistic effect. When bound to the oestrogen receptor subtypes ER and ER, methyltoxychlor (MTX) exhibited agonistic actions, but it exhibited antagonistic activity when bound to the androgen receptor. MTX is an organochlorine pesticide that was developed as an alternative to DDT [17, 18, 19]. It is effective as an insecticide.

It has been shown that the environmental pollutant known as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has an anti-androgenic impact in addition to acting as an antagonist of hormone production [20]. EDs have numerous hormone-binding activities, regardless of whether or not they bind to specific hormonal receptors. For instance, the chemical compound DDT acts as both an agonist for the oestrogen receptor and an anti-androgen [21]. In a similar fashion, BPA is an antagonist of the thyroid hormone, in addition to exhibiting estrogenic and androgenic action [22, 23]. Both thyroid hormone (TH) and thyroid stimulating hormone (TSH) have their mechanisms disrupted by BPA and other EDs, although in distinct ways. They do this by inhibiting the metabolism of these hormones, altering the action of the enzyme deiodinase, and preventing

thyroid cells from absorbing iodine. In addition, this led to the antagonism of complexes that arose from thyroid hormone responsive elements (TREs), as well as the competitive inhibition of the thyroid transport protein (TTR) [24, 25]. The particular TH-EDs, such as hydroxylated polychlorinated biphenyls (PCB) metabolites, brominated flame retardants, and dioxins (PCDD), have a structural similarity with TH. As a consequence, they are able to connect with TTR with a high degree of affinity, which results in the inhibition of -TTR binding [26, 27].

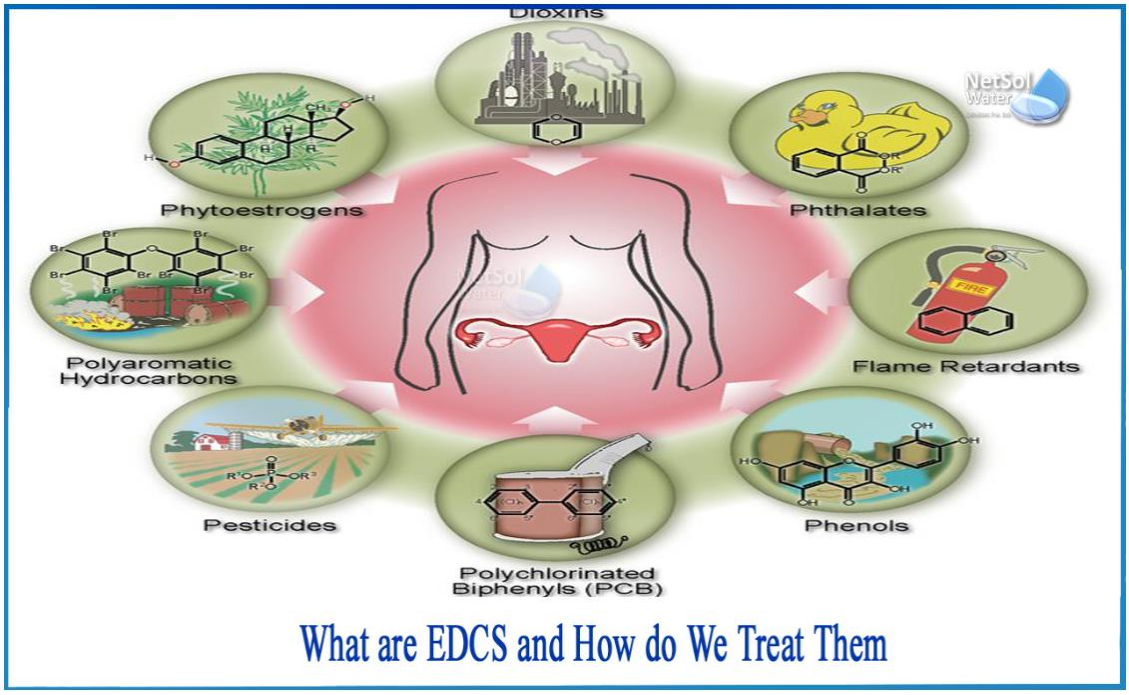

Fig 4. Effect of EDCs on human

RECEPTORS FOR ARYL HYDROCARBONS AFFECTED BY EDCs

At the molecular level, EDS is able to easily influence the enzymes that are connected to sexual hormones and the production of steroids. They accomplish this goal by affixing themselves to nuclear receptors and, as a result, inducing the transcription of genes corresponding to those receptors. It has been shown that dioxins and organochlorine pesticides have a strong affinity for the aryl hydrocarbon receptor (AhR). As a consequence, the expression of the CYP1 gene took place, which led to the conversion of estradiol (E2) into hydroxylated derivatives [28, 29]. The aryl hydrocarbon receptor, also known as AhR, may be found in the cytoplasm and interacts with

three different proteins. These proteins include the immunophilin-like protein XAP20, the chaperon protein HSP90, and the regulatory protein P23. When AhR binds to ligand, these regulatory proteins detach from AhR, allowing AhR to enter the nucleus. The role of these proteins is to make AhR sensitive to the ligand binding. It does this by forming a complex and a heterodimer with a protein called hydrocarbon receptor nuclear translocator (Arnt) in the nucleus [30]. The formation of the heterodimer allowed for the attachment of xenobiotic response elements (XRE), which are particular DNA enhancer sequences; the result of this was a speeding up of the endogenous hormone's metabolic process [31, 32]. The proteins and enzymes that are produced as a result of these gene sequences are of the growth-regulatory and drug-metabolizing varieties. Oncogenes, cytochrome CYP 1A2, CYP 1A1, CYP1B1 and P450 1A1 are the AhR-target genes that are most often the subject of discussion.

EFFECT OF EDCs ON METABOLISM AND HORMONE SYNTHESIS

Some EDs also have the effect of reducing the hormones' bioavailability in the body. These changes are brought about by EDs, which interfere with the transport and secretion of hormones in the body. Disrupting the enzymatic pathways that lead to the production and metabolism of hormones [34, 35] is another method for accomplishing this goal. For instance, oestrogen may be produced in either sex by androgens going via the aromatase pathway. Together, these two factors play an important part in maintaining homeostasis [36]. Phthalates and DDT are known to decrease aromatase activity, but BPA and atrazine have been shown to interfere with aromatase and increase its activity [34, 40]. Both BPA and phthalates are recognised as virilizing endocrine disruptors, and recent research has shown that both of these substances are potent inhibitors of cyclooxygenase. As a result, they lower the production of prostaglandins. This has the potential to be the most promising and major mode of action that these EDs use in order to display their effects [41].

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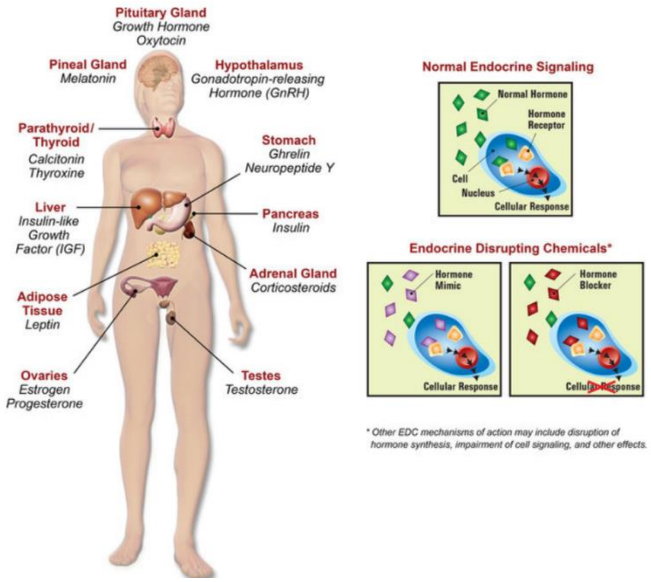

Fig 5. Effect of EDCs on hormone system

EPIGENETIC EFFECTS

The study of changes in gene function that do not include modifications to the DNA sequence is referred to as the research of epigenetic effects. Methoxychlor (also known as MTX) and diethylstilbestrol (often known as DES) are examples of EDs that could have this sort of impact. The effects of epigenetic modifications may be mediated through transcription factors, which can either stimulate or inhibit the transcription of certain genes. The key processes include post-translational changes of histone proteins, DNA methylation, and non-coding RNA [42, 43, 44]. DNA methylation was to blame for the decrease in gene expression, which was caused by a disruption in the DNA's normal interaction with the transcription factor [45]. Modifications made post-translationally to histone proteins have the potential to interfere with both the function and structure of chromatin.

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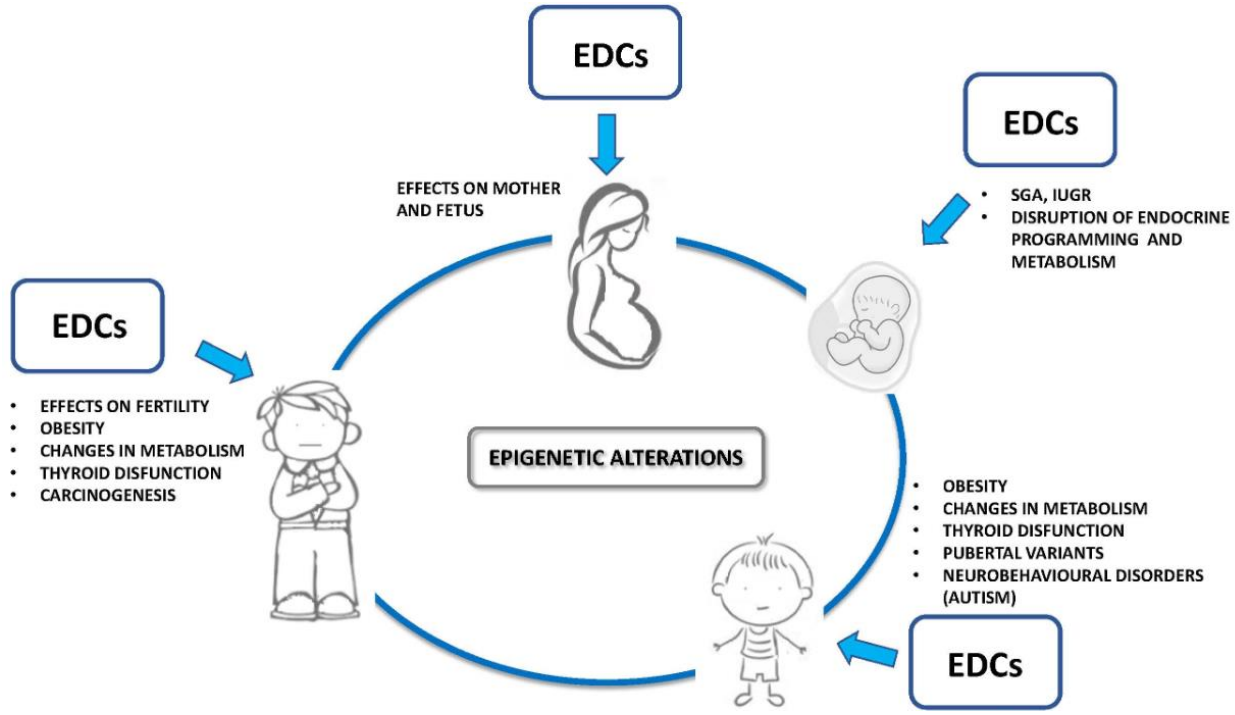

Fig 6. epigenetic diseases caused by EDCs

In the process of post-translational modification of histone, acetylation leads to the activation of transcription because it relaxes chromatin, while deacetylation results in the suppression of genes and, as a consequence, the transcription process. The role of regulating gene expression in both a cis and a trans way was performed by non-coding RNAs. Despite the fact that they contain gene sequences, the purpose of such sequences is not to code for protein but rather for control. [47] Research found that non-coding RNAs have a variety of activities, including genomic imprinting, developmental patterning and differentiation, as well as the inactivation of X chromosomes. When DES trigger the expression of genes at a young age, such as childhood, this might lead to the upregulation of genes involved in neonatal development, such as c-jun, c-myc, c-fos, and lactoferrin [48]. This impact was seen in the adult uterus and was caused by hypomethylation of the promoter region of the lactoferrin gene [49]. When individuals reach the same interval in maturity, however, such methylation is unable to take place [50]. The organochlorine pesticide MTX caused epigenetic changes to occur in the ovary, which were observed. As a consequence of its action, MTX leads to an increase in the amount of methylation in the ER promoter region. DNA

methylation is age dependant. Ribosomal proteins and transcription factors are two of the candidates for methylation by MTX on the genomic sequence [51].

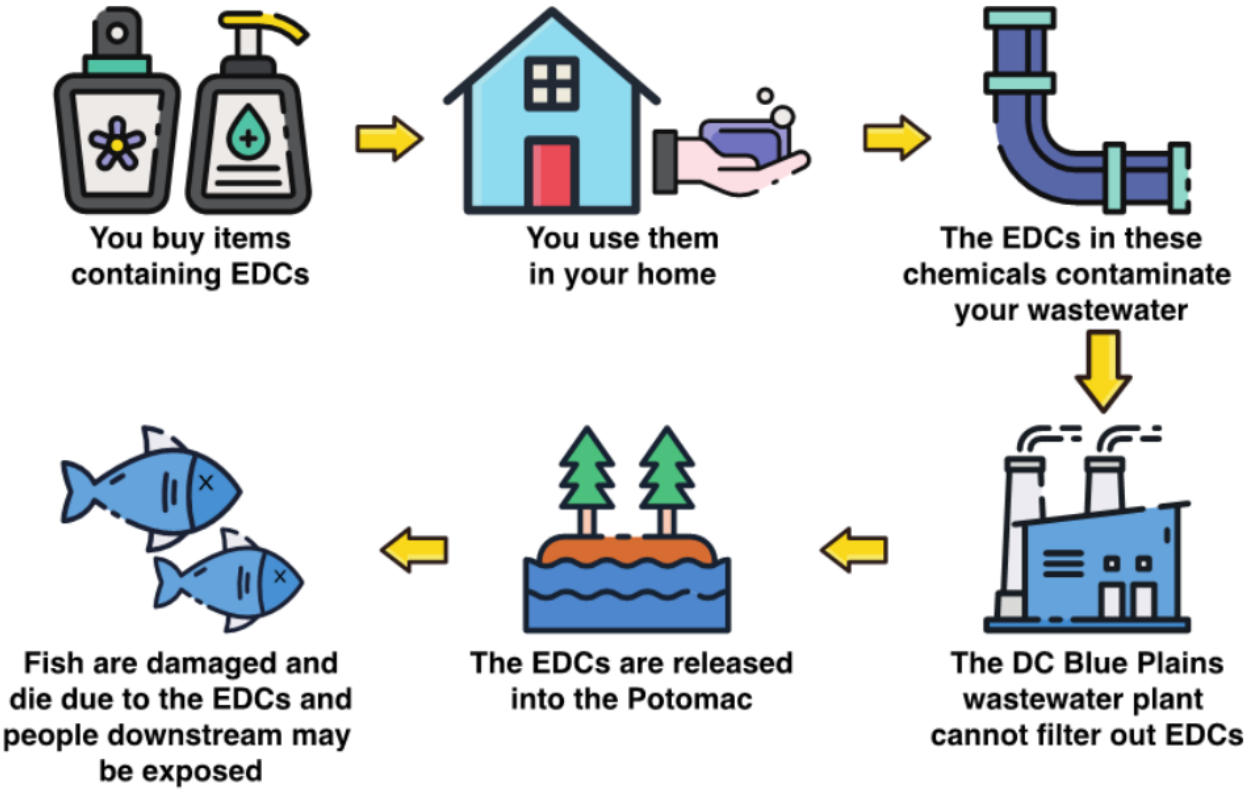

Fig 7. Flow sheet diagram for EDCs and their effect on animals

EDCs TREATMENTS

A depiction in the form of a schematic diagram of the in vitro and ex vivo research procedures that were applied to explore the effects of EDCs on TME. These approaches were used to find out how EDCs affect TME. It is possible that RACK1 might be used as a molecular tool for the purpose of researching the immune-correlated and tumorigenic consequences of EDCs. This is due to the fact that RACK1 is involved in a variety of important pathways relevant to both the immune system and the setting of cancer. While a strictly in vitro approach through cancer cells and immune cell co-cultures can benefit from genetic manipulation (i.e., stable transfection of both cell lines with a porter construct containing RACK1 promoter region), an ex vivo strategy that exploits patient-derived organoid models for a better TME mimicking could allow for the evaluation of EDC-

mediated effects on the extracellular matrix. This is because an ex vivo strategy makes use of patient-derived organoid models. This is due to the fact that an ex vivo technique makes use of organoid models obtained from the patient [52].

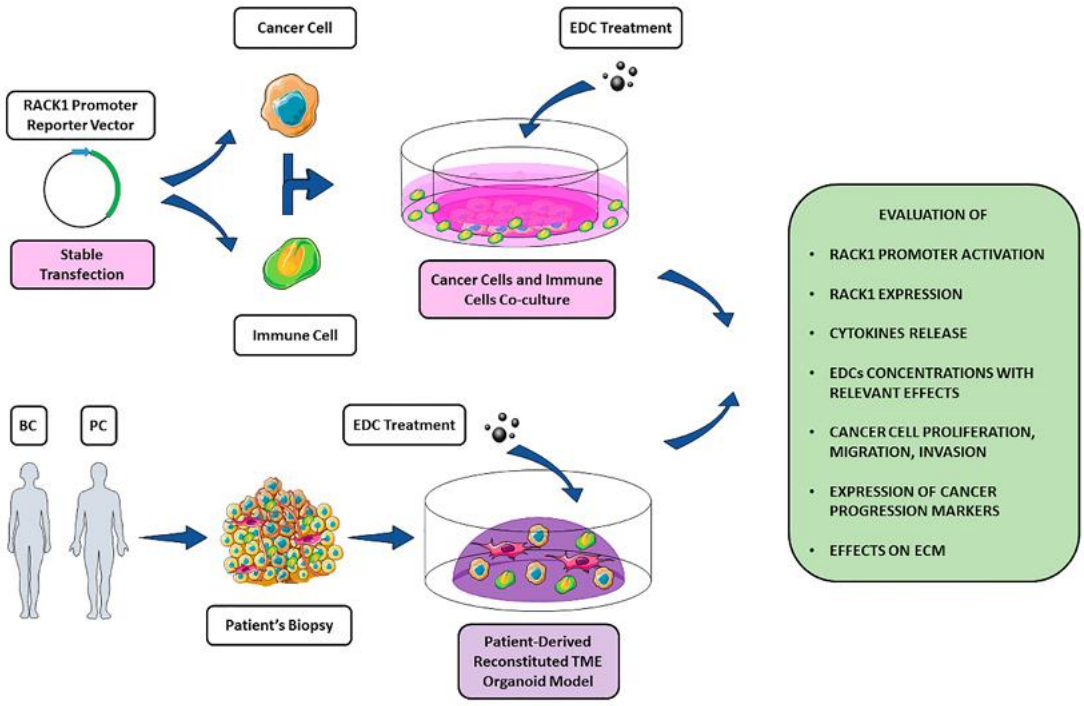

Fig 8. Ex vivo research procedures that were applied to explore the effects of EDCs on TME

CONCLUSION

This review study provides a concise summary of the chemical basis of EDs, as well as their basic properties and the mechanistic route of their action. Disruption of the endocrine system is a very serious threat to public health that cannot be disregarded. It is imperative that these harmful compounds be eliminated entirely from the environment. For instance, choose food that has not been treated with pesticides, switch from plastic to glass containers, and reduce the amount of fatty animal products you consume. Despite growing evidence linking these environmental factors to NCDs, it appears that the 2030 Sustainable Development Goals (SDGs) do not prioritize eliminating or at least reducing our reliance on synthetic chemicals. Despite the SDGs' justifiable

emphasis on air pollution and climate change as global objectives, reducing exposure to synthetic compounds with endocrine-disrupting or other harmful impacts is not an SDG. After analyzing tens of thousands of published studies, we have emphasized the complexity of the associations between exposure to environmental toxicants (EDCs) and illness and impairment throughout the life span. Numerous studies are cross-sectional in nature, and exposure assessment methodologies, especially for chemicals with short half-lives, are fraught with uncertainty, making it challenging to draw conclusions about associations between exposure and outcome. Innovative research instruments and methods may aid in resolving some of these problems. Prenatal studies that rely on a spot biospecimen during pregnancy or a given pregnancy period (for example, in assessing associations with trimester-specific exposure) are likely to have high attenuation bias and low power due to the high variability in BPA and other non-persistent chemical concentrations among individuals. Researchers should routinely collect biosamples from pregnant women throughout their studies to reduce the likelihood of measurement error. This will also enable the development of intermediate indicators capable of predicting disease endpoints and the cumulative effects of multiple interacting exposures. Genomic and related methodologies can be used to investigate interactions between genes (or gene expression) and exposures. It is very necessary for these EDs to have continuous study done on them in order to learn about their potential, dissemination, and mechanism of action.

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