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Mini Review

Endocrine Disrupting Chemicals and the Effects They Play in Plant Regulators

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Introduction

Over the past few decades, there has been increased global concern regarding Endocrine Disrupting Chemicals (EDCs). Endocrine disrupting chemicals, also known as Endocrine Disruptors (EDs), are chemicals that may interfere with the endocrine or hormonal systems in animals and humans. These chemicals can be manmade as well as naturally produced in the environment. While some chemicals have been found to be endocrine disruptors, mixed information and contradictory studies obscure the true severity of EDCs. In some cases, the data portrays endocrine disrupting chemicals as negative to human health and hazardous to the environment; examples of this include the research found against Bisphenol A. In the same nature, some EDCs or suspected EDCs like phytoestrogens are typically identified as helpful and beneficial. This review article aims to examine the mechanisms of regulation in endocrine disrupting chemicals and their effects on human health in efforts to shed light on some of the misconceptions often associated with EDCs.

How are EDCs Being Regulated Around the World?

Endocrine disruptors have become an international issue as different countries continue to take measures to regulate these chemicals. In 2018, the United Nations published a list of 45 chemicals which have been identified as endocrine disrupting chemicals or potential EDCs. The list was published by the International Panel on Chemical Pollution (IPCP) commission by the UN Environment [1]. The chemicals on this list have undergone a minimum of one "thorough scientific assessment [1]." Table 1 includes some of the items the UN listed as endocrine disrupting chemicals. Some categories, such as pthalates, have a specific distinction to indicate if they were placed on the list based on the EU Reach effort or if they were classified as an EDC based on other governmental organizations or entities. The majority of endocrine disrupting chemicals information and studies are conducted in Europe as well as the United States.

In Japan, programs such as Extended Tasks on Endocrine Disruption (EXTEND) and Strategic Programs on Environmental Endocrine Disruptors (SPEED) have been established in order to try and assess environmental risks caused by EDCs [2]. Japan does not publish an official list of endocrine disruptors; however it has composed a list of approximately 67 chemicals that they suspect act as endocrine disruptors [2]. In Europe, toxic chemicals and EDCs are regulated under Biocidal Product Regulation (BPR) and REACH Biocides laws [3,4]. The main goal of these organizations is to establish regulatory laws aimed at improving the biocidal products and chemicals being sold across Europe with an emphasis on protection of human life and environment [4,5]. As of 2017, the European Union (EU) began regulating several consumer products (e.g. cosmetics, packaging, toys, plastics) in order to reduce the possible exposure of endocrine disrupting chemicals [6]. In Australia, EDCs are regulated under Australian Pesticides and Veterinary Medicines Authority (APVMA). Although there is a general consensus across different countries on the definition of endocrine disrupting chemicals, there is not yet a definitive list of endocrine disrupting chemicals. Table 1 is a small example of what different governments consider to be EDCS or potential EDCs.

In the United States, the EPA is the governing organization that regulates EDCs. The EPA has taken several important measures to ensure the protection and safety of human life and wildlife. In August 1996, the United States Congress passed the Food Quality Protection Act (FQPA) [7]. This required the EPA to develop a screening program (EDSP) for possible endocrine disrupting effects. In October 1996, the EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), a federal advisory committee which made recommendations on how to develop the screening and testing program [7]. The purpose of this committee was to develop "consensus-based recommendations for a scientifically defensible screening program that would provide the EPA with the necessary information to make regulatory decisions about the endocrine effects of chemicals [8]." Due to a growing concern over endocrine disrupting chemicals and their potential harm, the EPA created OCSPP Series 890 - Endocrine Disruptor Screening Program Test Guidelines. Endocrine Disruptor Screening Program Test Guidelines are intended to meet testing requirements under The Toxic Substances Control Act (TSCA), The Federal Insecticide,

Table 1: A sample list of chemicals the United Nations has identified as possible EDCs. The full list can be found in the UN List of Identified Endocrine Disrupting Chemicals article [1].

Classification	Substance
4- Tert-Ocylphenols	4-(1,1,3,3- tetramethylbutyl)phenol; 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated
Pthlatates	Diisobutyl phthalate; DIBP; Dibutyl phthalate; BPP; Diethyl phthalte (DEP)
Benzophenones	Benzophenones
Bisphenols F and S	Bisphenol F; Bisphenol S
Parabens	Methylparaben; Ethylparaben; Propylparaben; propyl 4-hydroxybenzoate

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Table 2: This table takes a closer look at the different global organizations and what they classify as endocrine disrupting chemicals or potential endocrine disrupting chemicals. The majority of EDC studies that are currently being conducted are found in the United States and across Europe.

Country or Governing Entity	Organizations Responsible for EDC Regulation	Classification and Types of Chemicals	Examples of Endocrine Disrupting Chemicals
United States	• Environmental Protection Agency (EPA)	• Natural Hormones • Industrial Solvents • Certain Herbicides • Plastics Used in Commercial Products	• Bisphenol A • Dioxin • Atrazine • Phthalates
European Union	• Biocidal Product Regulation (BPR) • Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Biocides Laws	• Cosmetic Chemicals • Parabens • Phenol Derivatives • Herbicides	• Petrachlorophenol (PCP) • Benzophenone-3 • Tebuconazole • Resorcinol • Triclosan • Kojic Acid
Australia	• Australian Pesticides and Veterinary Medicines (APVMA)	• Natural Hormones • Pharmaceuticals • Phenols • Herbicides • Insecticides	• Pentachlorophenol (PCP) • Hexachlorocyclohexane, Ethyl Parathion • Di-N-Butyl Phthalate • Octyl Phenol • N-Butylbenzene
Japan	• Ministry of Environment Protection (MEP) • Strategic Programs on Environmental Endocrine Disruptors (SPEED) • Extended Tasks on Endocrine Disruption (EXTEND)	• Dioxins And Furans • Polychlorinated • Biphenyl • Herbicides • Insecticides	• Pentachlorophenol (PCP) • Hexachlorocyclohexane Ethyl Parathion • Di-N-Butyl Phthalate • Octyl Phenol • N-Butylbenzene
China	• China's Ministry of Ecology and Environment (MEE) • Inventory of Existing Chemical Substances (IECSC)	• Pesticides • Heavy Metals • Phthalates • PAHs	• Bisphenol Polybrominated Diphenyl Ethers (PBDE) • Tetrabromobisphenol A (TBBPA)

Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) to determine if a chemical substance may pose a risk to human health or the environment due to the disruption of the endocrine system [9].

What are Endocrine Disrupting Chemicals?

Some of the concerns revolving around endocrine disruptors are due to the potential interactions and interferences these chemicals may have with normal functions of the endocrine system. We believe that knowledge on the mechanisms of endocrine disruptors and their functions are still in the stages of infancy. Endocrine disruptors may function by mimicking hormones and binding to their receptors. It is also possible for endocrine disruptors to alter the synthesis, transport, binding and breakdown of hormones [10]. In some cases, endocrine disruptors may interfere with reproduction or reproductive systems, which may result in an increased cancer risk and disturbances in the immune system and nervous system function [10]. While there is some supporting evidence that endocrine disrupting chemicals can cause negative effects in wildlife, there is limited evidence for the potential of EDCs to cause these effects in humans at environmental exposure levels [9]. "The relationship of human diseases of the endocrine system and exposure to the environmental [contaminants] is poorly understood and seems scientifically controversial" [10].

There are different classifications of endocrine disrupting chemicals. They can be both manmade as well as naturally occurring. Examples of suspected endocrine disrupting chemicals include natural and synthetic compounds such as: organochlorine compounds, polychlorinated biphenyls (PCBs), fungicides, and some naturally occurring plant estrogens [10,11]. Fungicides are pesticides that help regulate and stop the spread of unwanted spores and fungi in plants. The majority of fungicides are categorized as having low toxicity. Fungicides are mostly used in agriculture to protect vegetables, fruits, and grasses. Common examples of fungicides include members of the azole family such as tebuconazole, propiconazole, and hexaconazole. Triazole fungicides are often critiqued and deemed as a possible endocrine disrupting chemical with possible connections to thyroid disruption [12,13], but the mechanisms in which triazole fungicides possibly mimic androgens or antiandrogens has not yet been resolved [14]. The regulation of these chemicals in different countries has also not yet been resolved. Tebuconazole is considered an EDC in Europe [1,4] while in the United States it is not considered an EDC. The United States has a different approach where chemicals are based on risk assessment.

Plant hormones substances such as auxins, gibberellins, cytokinins, abscisic acid (ABA), ethylene, and brassinosteroids are naturally occurring [15]. Similarly, plant hormones that act as endocrine disruptors are called phytoestrogens. Phytoestrogens are naturally-occurring substances that are structurally and/or functionally similar to mammalian estrogens and their active metabolites [16]. Phytoestrogens are found in several foods including: soy products, grains (such as wheat and alfalfa), fennel, celery and other crops. Plants use phytoestrogens to control and manage vital metabolic functions. Phytoestrogens also have several health benefits "including a lowered risk of osteoporosis, heart disease, breast cancer, and menopausal symptoms" [16,17].

Phytoestrogens are sometimes considered to be endocrine disrupting chemicals, as they function in a similar manner to human estrogen but they are considered to be much weaker than human estrogens [16,17]. Plants have secondary metabolites, often referred to as allelochemicals [18]. Allelochemicals are naturally occurring and are considered necessary for plant defense. Allelopathy is interference to plant growth that mediates from chemical interactions between plants and other organisms [18]. Important examples of allelochemicals include: phenols, alkaloids, terpenoids,

Table 3: The final results as determined by the EPA in regards to the toxicity and EDC effects of these triazole fungicides.

Chemical Name	Possible EDC Effects In Estrogen Pathways	Possible EDC Effects In Androgen Pathways	Possible EDC Effects In Thyroid Pathways	Risk Assessment To Be A Potential EDC
Tebuconazole	• *In vitro* and *in vivo* studies show possible interactions with the estrogen pathways	• *In vitro* studies show possible interactions with the androgen pathways • *In vivo* results only demonstrate a possible interaction in young mammals.	• Thyroid and Developmental findings are inconsistent with a direct, thyroid related delay.	Low Risk
Propiconazole	• In ER binding assays, propiconazole was not a binder to the estrogen receptor. • There is currently weak evidence to demonstrate this chemicals as an estrogen receptor or antagonist	• In AR binding assays, propiconazole was a weak binder. • Some *in vivo* reports indicate possible interaction with androgenic effects but testosterone levels were unaffected. There were no treatment related effects on sperm measurement or reproductive changes.	• There were findings of propiconazole effecting thyroid weights and no histopathological changes in the male or female rats.	Low Risk

benzoxazinoids, glucosinolates, and isothiocyanates [19].

What Role do Bioregulators Play?

Plant hormones or bioregulators have multifunctional effects; they are responsible for regulating plant growth and development. Having low or minimal toxicity also means having no negative impacts on the environment [15][20]. Brassinosteroids are important plant growth regulating (PGR) hormones that have a wide distribution throughout the plant kingdom and beneficial growth promoting activity when applied exogenously [22]. Brassinolide (BR) is an example of a naturally produced brassinosteroid. Brassinolide (2α, 3α, 22α, 23α-tetrahydroxy-24α-methyl-B-homo-7-oxa-5α-cholestan-6-one) is a plant growth-promoting steroid that is isolated from rape pollen [20,21]. Brassinosteroids act both independently and in conjunction with other phytohormones to control multiple physiological and developmental processes [23]. Brassinosteroids play a very important role in plant growth regulation and encompass several aspects including anther and pollen development [23]. BR possesses several beneficial qualities such as increasing the sensitivity of tissues up to 50-fold [21]. Additionally, brassinosteroids have been shown to increase yields and improve stress resistance of several major crop plants [24].

How Dangerous are Endocrine Disrupting Chemicals?

There is often concern regarding plant regulating chemicals and their possible endocrine disrupting effects over the impact they may have on the environment. These chemicals have faced additional scrutiny to ensure public and wildlife safety, and to minimize possible EDC exposure risk. In the United States, The Endocrine Disruptor Screening Program (EDSP) screens pesticides, plant growth regulating chemicals, and environmental contaminants on two tiers to evaluate their potential effect on estrogen, androgen, and thyroid hormone systems and ultimately establish if they are an EDC [25]. Tier 1 is used to identify possible or suspected EDCs. If the chemicals in Tier 1 demonstrated potential interaction to the hormone system, they continue for further evaluation in Tier 2 testing. Tier 2 involves a comparative thyroid assay for four chemicals that indicate interactions in the thyroid pathway of mammals, fish, amphibians, and birds [25,26].

In the specific case of brassinosteroids, the EPA concluded "that there is a reasonable certainty that no harm will result to the United States population, including infants and children, from aggregate exposure to residues of homobrassinolide applied/used as a plant growth regulator in accordance with good agricultural practices. Therefore, an exemption is established for residues of homobrassinolide in or on all food commodities when applied/used as a plant growth regulator in accordance with good agricultural practices [27]."

Additional studies have been conducted to find that brassinosteroids have minimal indication of being an endocrine disrupting chemical, if at all. In one study, the teratogenic potential of brassinolide was observed in Wistar rats [28]. In this study, Homobrassinolide (HBR) was given to Wistar rats during their gestation period. "Maternal and embryo-fetal toxicity was analyzed by studying the… clinical signs, mortality/morbidity, abortions, body weight, feed consumption, and pregnancy data, gravid uterine weights, implantation losses, litter size, external, visceral, and skeletal malformations [28]." Results from the study indicate that there is no treatment-related effects and concluded that HBR is nonteratogenic in dosages up to 1000mg/kg in Wistar rats.

In the case of fungicides, many questions have been raised in regards to the toxicity of triazole fungicides. As previously mentioned, the European Union classifies tebuconazole as an EDC, yet the United States does not. Some are worried that these chemicals are emerging contaminants [29] that lead to endocrine-disrupting effects. Table 2 demonstrates the actions and screening results the EDSP have established in regard to the potential for endocrine-disrupting chemicals. Their studies were based on the whether tebuconazole or propiconazole had the potential to interact with thyroid, estrogen, or androgen, hormone system. In both studies, the chemicals only underwent an EDSP Tier 1 screening. Tier 1 testing is "designed specifically to evaluate a number of key biological events including potential effects on receptor biding, steroidogenesis, and other effects on the HPG [25,26]."

The EPA did not deem these fungicides as dangerous enough to require Tier 2 testing. The EPA stated that Tier 2 testing is not recommended as "additional testing will not impact the current EPA established regulatory endpoints for human health risk [25,26]." After received EDSP Tier 1 screening, the triazole fungicides demonstrated that they did not directly act on estrogen, androgen, or thyroid systems. There is not strong enough evidence to support or recommend the need for further testing.

Discrepancies in the Severity of Endocrine Disrupting Chemicals

There have been several conflicting reports and studies in regards to the negative effects of endocrine disruptors. While some endocrine disruptors have been taken off of the market and are found to be dangerous, as in the case of diethylstilbestrol, there is still uncertainty on the severity of endocrine-related effects. Endocrine disrupting chemicals are found naturally in certain plant organisms, in everyday plastic use, cosmetics, medications, medical devices, any many more places.

Despite chemicals being regulated by the EPA, there is often still doubt in the true potential and harm caused by possible endocrine disruptors. In July 2020, CNN published a paper titled “Plastics and pesticides: Health impacts of synthetic chemicals in US products doubled in last 5 years.” The paper scrutinizes endocrine-disrupting chemicals and states that they cause a wide range of health effects – from cognitive deficits and obesity in children to breast cancer and prostate cancer in adults [30]. The paper makes several claims and portrays all endocrine disrupting chemicals, or possible EDCs in an extremely negative light. While there is evidence to support the harmfulness of endocrine disruptors, there are several studies that indicate that the severity of EDCs are not necessarily as dangerous as they are portrayed, and in some cases, they have little to negligible effects on human health.

Mr. Geoffrey Kabat, an epidemiologist, has discussed concerns over the validity and extent to which endocrine disruptors are truly harmful [31]. Upon examining the 2020 CNN article, Mr. Kabat found several discrepancies and misinformation published within the original article. Kabat notes that a major fact that the authors failed to acknowledge or recognize anywhere in their paper, is that the majority of the “exposures reported in the studies they review are to trace amounts of the various compounds [30]. Kabat proceeds to critically review the techniques and studies which were published in the paper and found conflicting information in the CNN article. Kabat goes on to discuss the inconsistencies in their methodology and the true impacts of endocrine-disrupting chemicals. In the original article published by CNN, four studies were cited and focused on prenatal exposure to organophosphorus pesticides and intellectual deficits in children. However, of these four studies, two of studies indicate some sort of negative effect due to EDs whereas the other two studies do not. The original authors promote this as strong evidence and harm caused by EDCs but even within their own studies, they received mixed conclusions and mixed data [30] [31]. Kabat acknowledges the validity and concern over EDCs but also calls into question the true harm and levels that are often reported in studies that perpetuate a negative portrayal of these chemicals.

In another study, Dr. Safe from Texas A&M University [32] recognizes that endocrine disruptors have been previously hypothesized to cause low sperm counts in male reproductive system as well as linked to cancer in females. However when looking at the results from several studies in North America, the data demonstrated that sperm counts have not decreased nor was there a large change in both male and female reproductive systems. Dr. Safe, like Kabat, notes that correlational studies of human diseases and their relationship with EDs will continue, and “positive correlations with some diseases will undoubtedly be made [32].” Yet it is important that the interpretation of these data be analyzed critically. Dr. Safe concluded the role of endocrine disrupting chemicals and the role that they play in human health has not been resolved, but the current evidence is not compelling.

The fear of endocrine disrupting chemicals may have also been perpetuated due to the belief in cocktail effects [33]. In 1996, Arnold et al, [34] hypothesized that several chemicals or substances were endocrine disrupting chemicals with very weak potency, but the combined exposure for these weak substances could be additive and synergistic, thus resulting in negative, adverse effects on the organism. Moreover, many similar theories of this nature have arisen over the years, [35,36], which lead to the theory of the Cocktail Effects. The notion that minor or minimal exposures to possible endocrine disrupting chemicals will have an additive effect and cause harm to both human health as well as lead to negative environmental impacts. These cocktail effects however are being studied, and it is highly suggested that the likelihood of these chemicals having additive negative effects on the endocrine system is next to impossible to occur. There is scientific evidence that support the theory that there is a threshold or a maximum limit of adversity that reproductive toxins can reach [37]. Experts have gone through the data and determined the synergism is extremely rare and unlike to happen [37,38]. This paints a larger picture, in which further studies need to be conducted to establish a more concrete relationship between EDC and human health before assuming all plant growing chemicals cause issues to both human and environmental health.

Conclusion

Examination of endocrine disrupting chemicals and the effect they have on human health as well as wildlife is a strong point of contention between scientists. Endocrine disruptors are found to be wide spread and very common in everyday life and objects. They are commonly used for agricultural, municipal, home and medical purposes worldwide. When examining naturally producing plant hormones, such as HBR, there is little to no indication that this chemical would cause damage to human health or wildlife. The concentrations and levels at which Homobrassinolide is found at are very weak and their cumulative effects, essentially negligible. When considering the effects of man-made chemicals similar to tebuconazole, exhaustive tests should continue to be executed in order to establish the true nature or severity of possible EDC chemicals.

Humans are exposed to these compounds, and due to their toxic properties, the consequences of this exposure on human hormonal-dependent pathologies are being established [38]. When it comes to human safety along with wildlife safety, one must measure the pros and cons, the benefits and the risks associated with each chemical. Further studies should be conducted in order to truly understand the lasting impact associated with Endocrine disrupting chemicals. As one author summarized it, it “appears strange how the supports of the ED hypothesis appear to be mesmerized by the idea that a handful of weakly acting chemicals that produce little or negligible human exposure must be somehow responsible for a range of hypothetical adverse effects on human reproduction or other human health problems [39].” While there is some evidence to suggest there is a hazardous effect of environmental EDCs on the endocrine system

[38,39], there is still an unclear relationship between the long-term effects of EDCs and human life. The best method moving forward would be to critically examine the mechanics and mechanisms of regulation in Endocrine disrupting chemicals, at what levels they impact humans and the environment, and how they affect humans.

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