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From past to present: a historical perspective of endocrine disruptors' impact on health and environment

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Abstract

Living organisms are exposed to a wide variety of chemicals that pose health risks. Endocrine disruptors (EDCs) are chemical compounds found in everyday products, food, medicines, pesticides, and other sources, with harmful effects on human health and wildlife. This review presents key historical milestones in understanding the biological effects of EDCs and the public policies implemented regarding their use. It describes the initial findings of damage caused by compounds used in industry, including polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), diethylstilbestrol (DES), dioxins, perfluorooctane sulfonates (PFOS), and others. It also covers the events that led to the term "endocrine disruptor" and the emergence of a new area of research in endocrinology. The role of scientific societies in obtaining experimental and association evidence is highlighted. The most relevant scientific statements on how EDCs affect health and promote disease are reviewed. Finally, advances in the regulation of EDCs are discussed, along with current challenges to their control and exposure.
Keywords: polychlorinated biphenyls, dioxins, diethylstilbestrol, endocrine disruptors, environment, human health.

Del pasado al presente: una perspectiva histórica del impacto de los disruptores endocrinos en la salud y el medio ambiente

Resumen

Los organismos vivos están expuestos a una gran variedad de sustancias químicas que representan un riesgo para la salud. Los disruptores endocrinos (EDCs) son compuestos químicos que se encuentran en productos de uso diario, alimentos, medicamentos y plaguicidas, entre otros; con efectos nocivos para la salud humana y la vida silvestre. La presente revisión comparte hitos históricos que han sido clave para comprender los efectos biológicos de los EDCs y las políticas públicas implementadas para su uso. Se describen los primeros hallazgos del daño inducido por compuestos empleados en la industria, entre ellos: los bifenilos policlorados (PCB), el diclorodifeniltricloroetano (DDT), el dietilestilbestrol (DES), las dioxinas, los sulfonatos de perfluorooctano (PFOS) y otros. Así también los eventos que dieron lugar al término "disruptor endocrino" y al surgimiento de una nueva área de investigación en endocrinología. Se destaca el papel de las sociedades científicas en la obtención de evidencia experimental y de asociación. Se mencionan las declaraciones científicas más relevantes sobre cómo los EDCs afectan la salud y promueven la enfermedad. Finalmente, se discuten los avances en la regulación de los EDCs y se mencionan los desafíos actuales para su control y exposición.
Palabras clave: bifenilos policlorados, dioxinas, dietilestilbestrol, disruptor endocrino, medio ambiente, salud humana.

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Introduction

Technological growth and development have favored the emergence of various chemical compounds that are necessary to satisfy basic human needs. However, many of them have harmful effects that pose a health risk to humans and wildlife (Encarnação, Pais, Campos & Burrows, 2019). In this context, growing scientific evidence has demonstrated the effects of environmental agents on health, leading to the coining of the term "human exposome," refering to the elements of the environment to which each individual is exposed in order to determine the potential risk to their health (Wild, 2005). Given the increasing prevalence of chronic diseases worldwide, research in this area has been proposed as an urgent task to identify the non-genetic factors underlying health and disease in the human population (Barouki *et al.*, 2022). The exposome considers the combined effects of factors such as lifestyle, ecosystem-intrinsic factors and collective and physicochemical factors, the latter being a substantial component that includes endocrine-disrupting compounds (Vermeulen, Schymanski, Barabási & Miller, 2020).

Endocrine disruptors or endocrine disrupting chemicals (EDCs) are defined by the Endocrinology Society as: "an exogenous chemical substance or mixture of chemicals that interferes with any aspect of hormone action at the level of synthesis, transport, metabolism and biological effects; consequently, causing adverse effects on an intact organism or its progeny / (sub) populations" (Zoeller *et al.*, 2012; Gore *et al.*, 2015).The term 'endocrine disruptor' originated from the observation of harmful effects in animals and humans exposed to certain chemicals (Colborn, vom Saal & Soto, 1993). For example, infertility in animals due to exposure to estrogenic compounds in food and pesticides such as dichlorodiphenyltrichloroethane (DDT) was reported as early as the 1940s, raising the first scientific concerns about the long-term health effects of these chemicals. The main route of exposure for EDCs is oral ingestion, once they enter the body, they are absorbed through the gastrointestinal tract and metabolized in liver, where they are inactivated and excreted. However, a small proportion of EDCs are not metabolized and remain in the bloodstream for 6-12 hours in the case of plasticizers, or in the case of persistent pollutants, they could be stored in body fat and cause various effects in the organism (Diamanti-Kandarakis *et al.*, 2009; Wang & Qian, 2021). EDCs act through various mechanisms of action, such as binding to hormone receptors, inhibition of hormone metabolism and synthesis, alteration of intracellular signaling pathways and cell proliferation/differentiation processes (Basak, Das & Duttaroy, 2020; Longo *et al.*, 2020; Kunysz, Mora-Janiszewska & Darmochwał-Kolarz, 2021).

In nature, we find natural EDCs such as phytoestrogens, like quercetin and genistein (Gore *et al.*, 2015). However, the vast majority of EDCs are substances of synthetic origin, used as plasticizers in various products (bottles, baby bottles, food packaging, pipes, etc.), emulsifiers in personal care products, food preservatives and cosmetics, for the coating of medicines, pesticides, insecticides, flame retardants or industrial detergents, to name a few (Guarnotta, Amodei, Frasca, Aversa & Giordano, 2022; Veiga-Lopez, Pu, Gingrich & Padmanabhan, 2018). Therefore, people are exposed daily to hundreds of products of synthetic origin every day, which together represent a heterogeneous population of chemical residues with potentially disruptive effects, that are difficult to remove from the market due to their ease of manufacture, low cost and wide use (Argemi, Cianni & Porta, 2005).

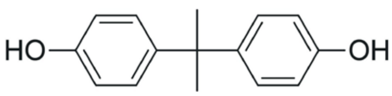
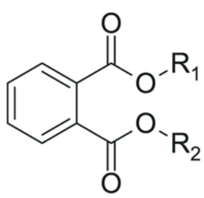
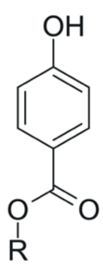
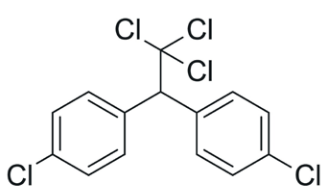
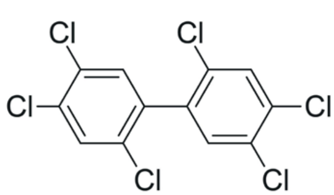
Other routes of exposure for EDCs are inhalation and dermal absorption (Kumar *et al.*, 2020). The life stage of the organism also determines the biological effects of EDCs. During pregnancy prenatal exposure can occur, in which both mother and child are exposed. Since EDCs can cross the placenta, they could affect the development of the fetus and have effects on early development or up to the adult stage of the organism (Catalán *et al.*, 2022).

In recent decades, more than 1,000 chemicals have been classified as EDCs and various biological effects related to their exposure have been described (Table I). In this context, a decrease in testosterone levels after exposure to some endocrine disruptors such as cadmium, phthalates and bisphenols or the reduction in sperm count associated with the use of pesticides has been reported in men (Yilmaz, Terekeci, Sandal & Kelestimur, 2020; Fittipaldi *et al.*, 2019; Gonçalves, Semprebon, Biazi, Mantovani & Fernandes, 2018). In addition, exposure to bisphenol-A (BPA), di-(2-ethylhexyl)phthalate, cadmium and pesticides such as hexachlorobenzene and DDT is associated with the development of polycystic ovary syndrome, endometriosis and the development of benign tumors and reduced fertility in women of reproductive age (Marlatt *et al.*, 2022; Souter *et al.*, 2013; Xu *et al.*, 2010; da Costa *et al.*, 2021).

On the other hand, metabolic changes due to exposure to EDCs have been reported. Prenatal exposure in pregnant women increases the risk of overweight and obesity in childhood and adulthood of their offspring. Similarly, adults exposed to phthalates and their metabolites, perfluorooctane sulfonates (PFOs) and perfluorononanoic acid, show an increase in adipose tissue which relates to obesity (Khan, Philippat, Nakayama, Slama & Trasande, 2020; Guerrero-Meza *et al.*, 2022).

In addition to the effects on the human population, the effects of endocrine problems on wildlife have also been studied. The main effect observed in fish, mice, invertebrates, amphibians and birds is reduced fertility, which leads to a decline in their population. However, thyroid problems, a reduction in the proportion of eggs hatched and changes in the immune system

Table I. Endocrine disrupting compounds in everyday use and biological effects associated with their exposure.

Endocrine disruptor	Belonging group	Product where it is located	Diseases associated with exposure	Exposure route	References
Bisphenol A 	Plasticizers	PS, PC and resins in aluminum cans, water bottles, thermal paper on purchase receipt.	Hypospadias, cryptorchidism, diabetes mellitus, heart disease, prostate and testicular cancer, obesity, thyroid disorders.	Orally	Gore *et al.*, 2015. Tuduri, Marroquí, Santos, Quesada, Fuentes & Alonso-Magdalena, 2018.
Phthalates 	Plasticizers	Buckets, toys, cosmetics, plastic jars, plastic medical instruments, PVC structures.	Cardiovascular diseases, diabetes, decreased sperm count. Respiratory disorders, neuro-developmental disorders, low birth weight during pregnancy	Orally Dermal absorption	Chang, Herianto, Lee, Hung & Chen, 2021. Wang & Qian, 2021.
Parabens 	Conservatives	Drugs (NSAIDs), foods (cereals), cosmetics and PCP.	Obesity. Alterations in male and female sex hormones, thyroid hormones, and glucocorticoids.	Orally Dermal absorption	Darbre & Harvey, 2008. Fransway *et al.*, 2019
DDT 	Pesticides	Insecticides for mosquitoes, flies, and ticks. It can contaminate food, soil, and water.	Cancer, chronic damage to the stomach, liver, obesity, alterations in the testicles and ovaries. Cardiovascular diseases.	Orally Inhalation Dermal absorption	Kabasenche & Skinner, 2014. Toft, 2014.
PCB 	Industrial additives	Oils, inks, carbon paper, paints, coolants, and lubricants in closed electrical equipment such as capacitors and electrical transformers.	Diabetes, obesity, decreased semen quality, thyroid disorders, liver carcinoma and androgenic and estrogenic disorders.	Orally Dermal absorption Inhalation	Christensen, Carlson & Lehmann, 2021.

have also been observed (Colborn *et al.*, 1993). In addition, the occurrence of intersexual specimens caused by the presence of tributyltin, triphenyltin and dibutyltin has even been reported in molluscs and arthropods (Marlatt *et al.*, 2022).

The first observed effects of EDCs

In the 1800s, polychlorinated biphenyls (PCBs) were first synthesized by Schmidt and Schultz and introduced to industry in 1929. Their key properties included their physical and thermal stability, as well as their resistance to acids and bases, which enabled their versatility in industry (Erickson, 2018). PCBs are synthetic chemicals composed of carbon, hydrogen and chlorine and are used in electrical equipment, plasticizers for paints and plastics, adhesives, heat transfer fluids, insecticides, wood coatings and other products (Dedrick *et al.*, 2012). The chemical properties of resistance to high temperatures and chemical stability favored the permanence of PCBs as environmental contaminants thus accumulating in water tanks or soils and endangering living organisms.

In the 1950s, a series of reported incidents demonstrated the risks of PCB exposure. In Brazil, a leak at a plant using PCBs caused an adverse reaction in two workers. In addition, painters at Monsanto Company fell ill after being exposed to PCB-containing paints in enclosed spaces. In a chemical plant in New Haven, Connecticut, some workers were also exposed to "organic acid A", which caused chloracne in the long term (Meigs, Albom & Kartin, 1954). On the other hand, when PCBs were used extensively as hydraulic fluids in machinery, the company "Bucyrus Erie" (Wisconsin) reported that workers exposed to these fluids suffered eye and facial burns (Markowitz, 2018). It is currently known that exposure to organochlorine compounds affect the endocrine system, particularly the thyroid and gonads, disrupting the reproduction of humans.

Regarding PCB exposure in wildlife populations, a study assessing the Baltic seal population found a decline from 14,000 to 4,000 individuals in about 20 years. One possible explanation for this phenomenon is PCB exposure, which leads to changes in the seals´ reproductive organs and sterility (Markowitz, 2018). In 1979, the production of PCBs was banned in the United States by the Environmental Protection Agency. However, their long half-life (12 days to 16 years) and presence in previously manufactured products makes them persistent organic pollutants (POPs) under the Stockholm Convention (Gore *et al.*, 2015). Nevertheless, the physical and chemical properties of PCBs, such as bioaccumulation in soil, uptake by crops, storage in body fat and their stability, continued to cause health problems for many years later after their ban (Gore *et al.*, 2015). Currently, PCBs levels are being monitored in urban environments in different countries in Europe and America. Data suggest that both adults and children continue to be exposed to these substances, which exceed levels previously established as safe and promote the development of leukemia, cognitive alterations and low birth weight (Rayhan, Akbor, Nahar, Chowdhury, Rahman & Saadat, 2024).

From 1925 to 1940, various subterranean clover species (*Trifolium subterraneum* var. Dwalganup) were sown in Australia as forage crops because of their economic advantages. However, after a year of cultivation and development, several farms reported problems with their sheep flocks. The flocks showed reproductive problems: infertility, complicated births in which the calf or mother died, and uterine prolapse. These incidents represented economic losses for the farms, as they recorded losses of almost 40% of the offspring at birth and losses in sheep that did not show clinical abnormalities. The affected sheep had a cystic endometrium with microscopic and macroscopic lesions caused by the high consumption of phytoestrogens in the diet (Bennetts, Underwood & Shier, 1946; Darbre, 2019).

From 1947 to 1954, it was known that the hormonal system of cattle influences their growth and thus also muscular development. Consequently, Purdue College investigated the use of diethylstilbestrol (DES), a potent synthetic estrogen, in cows, which resulted in a 15% increase in body weight. In 1954, the U.S. Food and Drug Administration (FDA) approved the use of DES in livestock as an additive to improve meat production; despite the improved performance, however, farmers found that meat quality declined with differences in fat content (Harris & Waring, 2012). As can be seen, the sources of exposure to EDCs varied, as did their effects, ranging from endocrine to economic problems in the cattle and industrial sectors.

Findings on human and animal health

In 1948, a study conducted by Smith suggested the possible use of DES in pregnant women to prevent complications such as spontaneous abortions (Smith, 1948). Subsequently, it was prescribed in the first trimester of pregnancy in women with threatened abortion, and it was also employed as hormone therapy in women, to treat prostate cancer in men, and breast cancer in postmenopausal women. In 1971, Herbst and collaborators demonstrated DES adverse effects as a treatment for pregnant women by observing gonadal alterations, an increase in the incidence of vaginal adenocarcinoma in daughters of women treated with the chemical compound, and a decrease in sperm count, hypospadias, and cryptorchidism in male children (Herbst, Ulfelder & Poskanzer, 1971). DES was identified as a carcinogenic substance and the FDA banned its prescription and use in humans in 1971 (Darbre, 2019; Harris & Waring, 2012), and its use in livestock was banned in 1979 (Harris & Waring, 2012).

Despite the information gained in previous years, there was still a lack of knowledge about other products for both medical and agricultural use. Regarding the latter, the nature of pesticides evolved until the development of synthetic pesticides in the

1900s, such as DDT, which had advantages over other chemical compounds, such as its low water solubility, which prolonged its half-life in the environment, its low cost, and its persistence in crops (Kabasenche & Skinner, 2014). DDT was used in agriculture for 50 years until its harmful effects on wildlife, especially birds, were discovered. DDT has been found to accumulate in the tissues of birds such as golden eagles, bald eagles and pelicans, negatively affecting their reproductive process (Colborn *et al.*, 1993; Mohanty, 2024; Rogers, 2016). Similarly, there is also evidence of contamination of various drinking water sources with different substances classified as EDCs, some of the affected areas are the Klang River estuary, Langat River, Putrajaya and Malaysia (Yuniarto & Hadibarata, 2024).

EDCs can affect many metabolic pathways or systems in the organism. Some of the most important biological processes affected are reproduction, metabolism, fetal development and the hormonal axis.

Reproduction

One of the most well-documented effects of endocrine disruptors is their negative impact on the reproductive system, both in men and women. EDCs can impair the production and function of sex hormones such as estrogens and androgens, leading to a variety of reproductive disorders. In men, reduced sperm quality and quantity and increased rates of infertility and urogenital malformations, such as incomplete descent of the testes or the development of testicular cancer, have been observed. In women, exposure to EDCs such as phthalates, BPA and pesticides has been associated with menstrual cycle disorders, infertility, endometriosis and an increased risk of miscarriage (Gore *et al.*, 2015).

Effects on fetal and neonatal development

Fetal development period is particularly critical due to the increased sensitivity to hormonal changes. During pregnancy, exposure to EDCs such as PCBs or DES can significantly alter the endocrine development of the fetus, leading to adverse effects that may not manifest until adulthood. EDCs can cross the placenta and reach the fetus, where they alter hormone signaling at crucial stages of development and affect the formation of the reproductive organs, nervous system and metabolism. In addition, studies have shown that prenatal exposure to certain EDCs is associated with early pubertal development in girls, a risk factor for various health conditions such as breast and ovarian cancer, and alterations in neuroendocrine behavior (Gore *et al.*, 2015).

Effects on metabolism and obesity development

In relation to obesity, the EDCs that can alter adipose tissue homeostasis and adipogenesis are referred as environmental obesogens. This term was coined by Grün and Blumberg in 2006 when they described the obesogenic effects and mechanisms of action of tributyltin, used as an insecticide and biocide, in boat paints and as a wood preservative (Grün & Blumberg, 2006). Similarly, *in utero* exposure to the plasticizer BPA has been associated with weight gain in rodents (Miyawaki, Sakayama, Kato, Yamamoto & Masuno, 2007). On the other hand, in a prospective study, BPA and butyl phthalates or di-(2-ethylhexyl) phthalates were associated with the risk of type 2 diabetes (Sun *et al.*, 2014). Exposure to phthalates and BPA has been associated with increased accumulation of adipose tissue, altered insulin sensitivity and increased prevalence of metabolic syndrome. These effects are not only observed in adults, but early exposure during fetal development or infancy predisposes individuals to obesity and type 2 diabetes in adulthood (Dalamaga *et al.*, 2024; Gore *et al.*, 2015).

Cancer and hormonal disorders

Exposure to endocrine disruptors is associated with an increased risk of developing hormone-dependent cancers such as breast and prostate cancer. EDCs can mimic the effects of sex hormones, such as estrogens, and thus contribute to the uncontrolled proliferation of cells in hormone-sensitive tissues. Exposure to compounds such as pesticides and phthalates has been shown to be associated with an increased risk of breast cancer in women and prostate cancer. These effects may be exacerbated by prolonged exposure to low levels of EDCs, challenging traditional toxicology paradigms that assume only high doses have harmful effects (Gore *et al.*, 2015; Hassan *et al.*, 2023).

All the information published about environmental problems attracted the attention of society, which included people who supported environmental movements. In this regard, the writer Rachel Carson published books outlining the importance of the harm of chemical compounds to the environment, such as "Silent Spring". The text essentially dealt with the problems associated with the use of DDT and the impact of human activity on the environment. Thanks to the impact of Carson's publications and the work of various environmental movements, DDT was banned in the United States and many parts of the world in 1972 (Carson, 1962).

Concern and first preventive measures

In the late 1970s, the existence of EDCs was common knowledge, as was the documentation of numerous case studies in animals and some accidents involving humans, so the governments of different countries began to be concerned about the problem and attempted to introduce regulations on the use of EDCs.

Due to industrialization and the growth of various chemical industries, accidents involving endocrine disruptors occurred. One example of this is the ICMESA plant in Meda, Italy, owned by Roche. The industrial plant was responsible for the production of chemical substances used in cosmetic, pharmaceutical and agricultural products. On July 10, 1976, during the synthesis process of 2,4,5-trichlorophenol, an unexpected chain reaction occurred, releasing components such as TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), sodium hydroxide, trichlorophenate, ethylene glycol and others. The surrounding population was alerted to the problem a week after the incident, whereupon the entire population was forcibly evacuated and studies were conducted on the health effects of those exposed to the chemicals (Centemeri, 2010). The results showed a link between exposure to dioxins and the development of chloracne, cancer and cardiometabolic problems, as well as a decrease in fertility in the exposed population (Centemeri, 2010).

Dioxins are a group of compounded polychlorinated chemicals (up to 75 different compounds) that are released as unwanted by-products of various industrial processes, e.g. herbicide and pesticide production, waste incineration and paper production after a chlorine bleaching process (Kanan & Samara, 2018). Due to their toxicity, long half-life (months to years) and considerable persistence in the environment combined with their ability to bioaccumulate they are considered POPs (Gore *et al.*, 2015). Their harmful effects include damage to the immune system, developmental disorders and reproductive problems in animals (Rysavy, Maaetoft-Udsen & Turner, 2013).

In 1980 a decline in male lizards was observed in Lake Apopka, Florida, USA. This decline was linked to the presence of DDT in the water, and this was demonstrated by observing the estrogenic and antiandrogenic effects of DDT leading to gonadal alterations in male lizards (Guillette, Gross, Masson, Matter, Percival & Woodward, 1994; Matsushima, 2018). On the other hand, dichlorodiphenyldichloroethylene (DDE) and PCBs have been reported to accumulate in the blubber layer of Dall's porpoises, a cetacean species. Likewise, elevated DDE levels have been associated with a decrease in plasmatic testosterone, which could impair sexual function (Subramanian, Tanabe, Tatsukawa, Saitao & Miyazaki, 1987; Guarnotta *et al.,* 2022). In some cases, a single exposure early in development was sufficient to cause effects on the embryo. For example, male Sprague-Dawley rats exposed to a single oral dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), (15 µg TCDD/kg) were found to have reduced plasma concentrations of testosterone and dihydrotestosterone and reduced seminal vesicle and prostate weights (Moore, Potter, Theobald, Robinson & Peterson, 1985; Colborn & Clement, 1992).

It was not until 1991 that the term "endocrine disruptors" or "EDCs" was coined at a conference in Wingspread, Wisconsin. This working conference, led by zoologist Dr. Colborn, brought together scientists from various disciplines to analyze the scientific evidence of the effects of synthetic chemical compounds on birds, fish, amphibians, reptiles, crustaceans, mammals and humans. The scientific evidence showed the consequences of about 500 environmental chemical pollutants such as dioxins, DDT, dicofol, kelthane, methoxychlor, DES and PCBs on the endocrine system of various organisms (Colborn *et al.*, 1992; Colborn *et al.*, 1993). This resulted in harmful effects on reproduction, organ differentiation and development, growth retardation and memory problems, strongly suggesting an alteration of hormone-dependent signaling pathways by EDCs, such as activation/inhibition of hormone receptors.

Current findings and response strategies

In 2002, the World Health Organization (WHO) produced a report compiling scientific evidence on the effects of EDCs on wildlife and humans. In this document, the WHO noted that there was insufficient scientific information to link exposure to suspected EDCs to human and wildlife health and reported areas of opportunity to clarify uncertainties in this new area of research, such as conducting further studies on mechanisms of action, effective concentrations, identification of biomarkers, and identification of EDCs (IPCS, 2002).

In 2009, the American Endocrine Society published its first scientific report on EDCs, providing information on research and discoveries on the nature of EDCs, mechanisms of action, and biological effects on endocrine systems (Diamanti-Kandarakis *et al.*, 2009). Similarly, experimental evidence for the transgenerational effects of EDCs was published, as in a study by Anway, Cupp, Uzumcu & Skinner (2005), in which they exposed a pregnant female rat to vinclozolin, a fungicide for agricultural use in vegetable crops, which produced in the F1 generation an adult phenotype with low spermatogenic capacity and male infertility. These effects were observed in most males of later generations (up to the F4 generation), which was related to alterations in DNA methylation patterns in the germline (Anway *et al.*, 2005; Anway & Skinner, 2008). On the other hand, the adverse effects of prenatal exposure to DES might be transmitted to subsequent generations, as a greater susceptibility to the formation of malignant tumors of the reproductive tract was observed in the offspring of mice treated with DES during different stages of development (gestation and neonatal period), (Newbold, Hanson, Jefferson, Bullock, Haseman & McLachlan, 1998). The first Endocrine Society statement called on the entire scientific community to conduct more targeted studies to determine the health effects of EDCs and their relationship to disease development (Diamanti-Kandarakis *et al.*, 2009).

In 2012, the European Society of Endocrinology (ESE) expressed its concern about the impact of endocrine disruptors and their effects on human health. The ESE, together with the European Commission, the European Food Safety Authority (EFSA) and other European governmental organizations for chemical management, published a statement on EDCs, highlighting the need for stricter regulation and the promotion of research in this field (Zoeller *et al.*, 2012). This statement emphasizes the importance of regulating the use of endocrine disruptors in the manufacture of products intended particularly for vulnerable populations such as children and pregnant women. This information was updated in 2017 to facilitate the identification of insecticidal and biocidal EDCs (Brito Jorge, Maria Luce & Ortiz García, 2020).

In the same year, the WHO published a detailed and updated report on the effects of EDCs on human health and wildlife. The WHO defines EDCs as "a substance or mixture that interferes with the function of the endocrine system and, consequently, causes adverse health effects in an organism or its offspring." In addition, it mentions the main concerns regarding exposure to EDCs, such as the effects on early development and reproduction, the incidence of endocrine system alterations in humans and wildlife, and the identification of new EDCs, and emphasizes the importance of continued research and the development of measures against exposure to endocrine disruptors (WHO, 2012).

Subsequently, a second Endocrinology Society statement was published in 2015, summarizing the scientific evidence for the association between exposure to EDCs and diseases such as obesity, diabetes, female and male reproduction, hormone-sensitive cancer in women, prostate, thyroid, neurodevelopment and neuroendocrine systems at the molecular, cellular and physiological levels, which overall strengthens the evidence for the biological effects of EDCs in relation to endocrine systems (Gore *et al.*, 2015).

Furthermore, the statement shows that the effects of EDCs depend on the susceptibility of the developmental stages of the organisms, the dose and the exposure time. Finally, the statement recommends greater regulation of the use of existing EDCs and avoiding the inclusion of new EDCs to replace them, so that new compounds must be fully evaluated to determine their biosafety before they are introduced into the industry (Gore *et al.*, 2015).

Finally, in 2020, the Endocrine Society published a report describing the effects of plastics on human health. Plastics threaten public health as they contain EDCs such as bisphenols, alkylphenols, perfluorinated compounds, brominated flame retardants, dioxins, phthalates, lead and cadmium. Therefore, it is necessary to regulate exposure to these EDCs and analyze numerous compounds found in plastics whose biological activity and effects on human health and wildlife are unknown (Flaws, Damdimopoulou, Patisaul, Gore, Raetzman & Vandenberg, 2020).

As can be seen in Figure 1, the scientific knowledge gained throughout history about the health problems and environmental impacts associated with exposure to EDCs has favored the involvement and consultation of scientific and regulatory organizations in the development of government regulations to control chemical compounds in daily use and in personal care products, food, pesticides and many others. In this sense, the ESE and the American Association of Clinical Endocrinology (AACE) are two international organizations that have addressed the impact of EDCs on human health. Both organizations have issued statements and recommendations to address the risks associated with these chemical compounds (Zoeller *et al.*, 2012; Gore *et al.*, 2015; Gore, La Merrill, Patisaul & Sargis, 2024).

The ESE is particularly concerned with the publication and dissemination of information relevant to education and awareness of the risks of EDCs to public health. While lAACE supports further research to understand the molecular mechanisms and long-term effects of exposure to EDCs, it also strives to develop policies that reduce human exposure to these substances, particularly in healthcare and products intended for children. The scientific opinion has allowed us to set new safe exposure limits for the population, which are constantly updated and reduce human and environmental exposure to EDCs. One example of this is the change in the tolerable levels of BPA intake in humans from 4 µg/kg/day in 2015 to 0.2 ng/kg/day in 2023 based on scientific evidence demonstrating the harmful effects of exposure to doses of BPA lower than those previously permitted (EFSA *et al.*, 2023). Recently, the European Commission (EU) issued a ban on BPA and all bisphenols with hazardous classification in all food containers such as plastics, paints, coatings, inks, adhesives, silicones and others and set a "non-detectable" limit for migration from products of <1 µg/kg (EU, 2024).

As seen, the European Union and the United States have introduced specific regulations to control exposure to EDCs through various regulations for pesticides, industrial chemicals and consumer products. However, enforcement of these regulations remain a challenge, primarily due to a lack of cooperation between industry and scientific sectors. EDCs do not affect just one industry sector, but are present in products as diverse as cosmetics, food packaging, textiles, detergents and pesticides. Therefore, regulation covering all possible sources of exposure is very complex as different economic sectors are subject to specific regulations. In addition, many of these products and substances are traded globally, which makes regulation and monitoring even more difficult.

Mexico could follow the example of the European Union and develop a regulation similar to REACH regulation (Registration, Evaluation, Authorization and Restriction of Chemicals), which covers the identification, evaluation and control of endocrine disruptors in consumer products, pesticides and industrial chemicals. In addition, it would be necessary to introduce specific risk assessment protocols for EDCs and a mechanism requiring manufacturers to demonstrate the safety of their products before they are placed on the market. Most importantly, more investment is needed in scientific research on EDCs, particularly epidemiological and toxicological studies that assess the local impact of these chemicals on human health

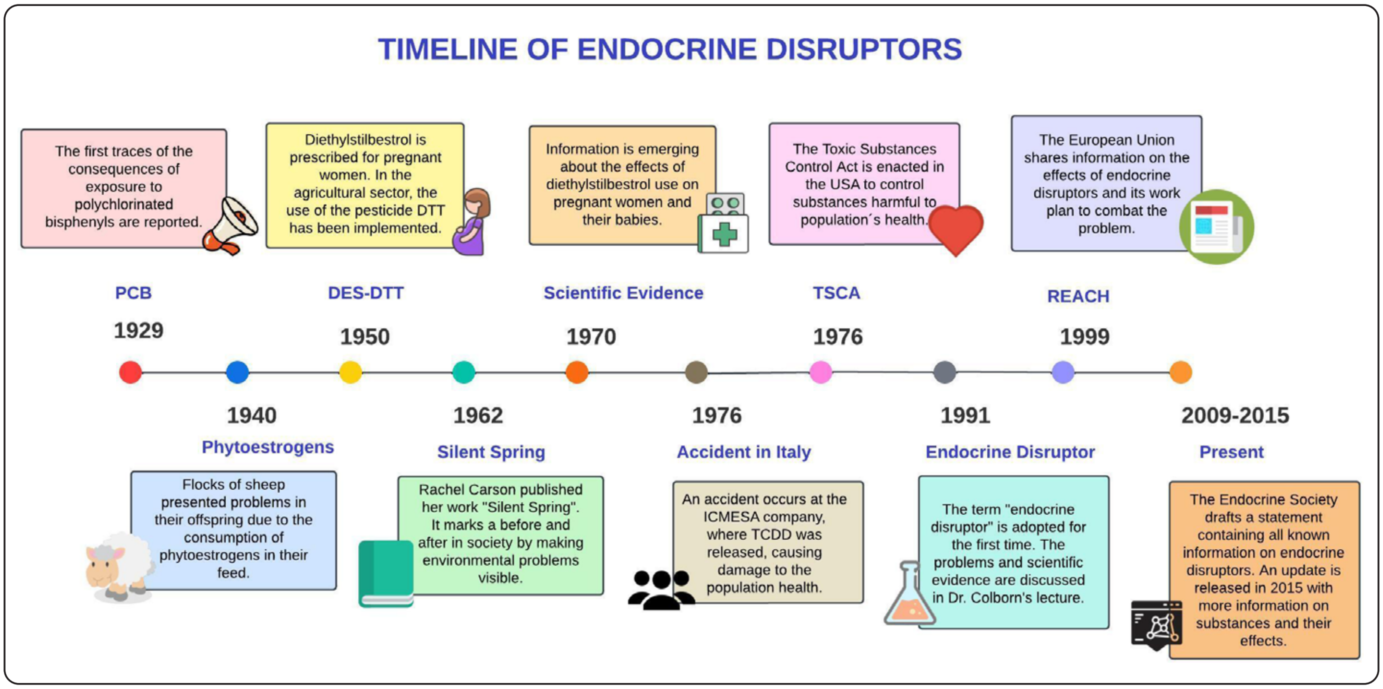


Figure 1. History of endocrine disruptors discovery. Historical milestones regarding the impact of EDCs on human health and the environment (Image created by authors).

and the environment. It would also be important to develop technologies that can efficiently detect these chemicals and their adverse effects, and support research that can impact regulation at the national level.

Great progress has already been made in the field of EDCs. It has been possible to identify the human exposure limits, the mechanisms of action and the endocrine, nervous and metabolic effects of these substances. Progress and scientific research are aimed at developing new systems for detecting endocrine disruptors and investigating the effects on other systems such as the cardiovascular system.

Conclusions

Endocrine disruptors have been present in our society since the 19th century, but were only recognized as such through the observation of their harmful biological effects on living organisms. The physicochemical properties of EDCs favor their use and presence in many commonly used products such as plastics, personal care products and even food and medicines, resulting in constant exposure to EDCs throughout human life. The consequences of exposure to endocrine disruptors are diverse and include metabolic, reproductive, inflammatory and behavioral disorders, among others.

Knowing the historical milestones that have led to the identification, characterization and understanding of the effects of EDCs on health and the environment allows us to identify areas where we can apply regulations against the problems arising from the use of EDCs in industry to prevent their biological effects on humans and other living organisms. Likewise, scientific evidence throughout history demonstrates the importance of assessing the biosafety of the chemical compounds used to manufacture synthetic products and emphasizes the need for a better understanding of the mechanisms of action, bioavailability and effects in different biological contexts.

In Latin America, it is essential to introduce regulations on the use and production of known EDCs in daily products, food and pharmaceuticals, as it has been observed their environmental exposure is higher than in other regions. There is also a need to develop policies and procedures to assess novel chemical substances or their mixtures in products for the pharmaceutical, toys, food or hygiene industries among others, that represent a direct exposure to the human population. Furthermore, it is an urgent concern to reduce EDCs-containing residues, such as in plastics, which are currently a global problem for human health and wildlife.

Current scientific efforts are enabling the public to become aware of the problem and participate in the implementation of preventive measures. Multidisciplinary work between scientific societies, governments and environmental movements has been key to provide scientific information to the public and to implement regulations aimed at suppressing and reducing the harmful effects of disruptors on humans and wildlife.

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