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Review Article

Endocrine Disruptors Regulatory Waves: A Frictional Lens Perspective on Regulated and Emerging Markets

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are significantly costing humanity, which upshots the increase in disease and disability. However, unlike other toxicant classes—EDCs have yet to be cataloged onto regulations in a mature way across the globe. This manuscript intends to serve up as a compendium of information that endows with an overview of existing regulatory frameworks and policies those deal with EDCs. In particular, it spotlights on frameworks that explicitly address EDCs (i.e., frameworks that consider both adverse effects and their endocrine causes in the assessment of chemical(s)). Precisely frameworks from 12 countries have been acknowledged, and information crucial to understanding the basic functioning has been summarized (including the scope and general procedures/practices relevant for EDCs, criteria, and data requirements). An attempt has been made to scan not only economical, regulatory policies available for regulated (USA, Europe, Australia, and Japan) and emerging markets (China, Brazil, South Africa, India, Bangladesh, Korea, and Malaysia), but also illustrate perspective for improvement.

INTRODUCTION

In recent times, EDCs compounds have acquired an interest in human physiopathology. An increasing number of studies planned to clarify how these synthetic substances influence the endocrine framework.^[1] Endocrinology is the part of medicine that focuses on endocrine organs and chemicals in the body,^[2] and the endocrine framework works through chemical messages (hormones) discharged from organs straightforwardly into the circulatory system to control the working of the distant objective organ. Feedback circles attempt to keep up the release of these chemicals, to keep up the homeostasis, i.e., the situation of consistent conditions which is imperative for life.^[3] Many synthetic substances, both natural and human-made, may decrease or influence the body's chemicals, known as the Eds.^[4-5] These synthetics are connected

with developmental, regenerative, cerebrum, immune,^[6-7] diminishing in sperm counts and other issues'. In 2012, UNEP and WHO, as a team with global specialists, have stepped forward by supporting the advancement of rules on endocrine disruptors.

A breakdown in the endocrine frameworks is made from EDs compounds (the organs, hormones, receptors, or organs affected by hormones) that can result in an endocrine disorder.^[8] The different dysfunctions can cause wide-going consequences for the body. The problems emerge from the large number of impacts brought about by excessively little or a lot of discharge of a hormone.^[9] Law and science combine in the estimation of risks from endocrine disruptors (EDs) and actions for their regulation in the pharma environment. The evidence that leads to either regulations or judicial decrees is affected by

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uncertainty and limited knowledge, raising complex policy issues.^[10] The regulatory frameworks available across major regulators are tackling the identification of EDs and their mechanisms to provide necessary guidance on the safety and disposal of such substances. Regulators of healthcare and environmentalists need to collaborate amongst them and with wider stakeholders, including industry sponsors, to find ways to deal with such challenges and capitalize on the research-based knowledge grid available across institutions.^[11]

ENDOCRINE DISRUPTORS (ED)

EDCs are considerably costing society because of expansions in sickness and disability.^[12] Global concerns have been brought up recently over the potential unfriendly impacts that may result from unveiling synthetic compounds that can influence the endocrine framework in wildlife and humans.^[13-14]

EDs are found in numerous ordinary items, including some plastic jugs and containers, liners of metal food jars, cleansers, food, toys, beautifiers, pesticides,^[15-16] and brominated fire retardants.^[17] The significant worries with ED in the climate generally depend on impacts that have been seen on the undeveloped organism and fetus.^[18]

Some EDCs demonstrate like "hormone mimics" and trick our body into imagining that they are hormones, while other EDCs block genuine hormones from managing their work. Other EDCs can increment or reduce the degrees of hormones in our blood by influencing how they are made, separated, or deposited in our body. Finally, other EDCs can change how sensitive our bodies are for different hormones.^[8]

There is valid justification to speculate that expanding chemical manufacturing and use is identified with the developing rate of endocrine-related pediatric issues in the course of recent years, including male regenerative issues (cryptorchidism, hypospadias, malignant testicular growth), early female pubescence, leukemia, cerebrum cancer^[19] and neurobehavioral disorders. Simultaneously, the worldwide creation of plastics developed from 50 million tons during the 1970s to almost 300 million today, and deals for the worldwide industry of chemicals have forcefully expanded from USD 171 billion out of 1970 to over USD 4 trillion in 2013.^[20] In 2019, the chemical industry's absolute overall income remained at some 3.94 trillion US dollars.^[21] Chemicals, such as polychlorinated biphenyls (PCBs), BPA, and phthalates, are currently noticeable in serum, fat, and umbilical cord blood in people worldwide. Truth be told, the idea of "better living through science" was presented by the chemical industry during the 1930s. This unavoidable idea underlies the worldwide increase in chemical substance production.^[22]

Various worldwide healthcare associations additionally have accepted the call for improved EDC approaches. In February 2013, the World Health Organization (WHO)

and United Nations Environment Program (UNEP) initiated their joint 2012 report on the study of EDCs. The report plots the current comprehension of EDCs and their impacts on human wellbeing; it also prescribes improved testing and decreased exposure to EDCs. Additionally, in 2013, the "Collegium Ramazzini"—an international foundation of eminent occupational and environmental health specialists – gave a declaration on EDCs in the European Union, requiring the development of the extent of the "Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH)" enactment and more comprehensive evaluation of the logical proof in administrative decision making. Again in 2013, an enormous gathering of independent researchers gave the "Berlaymont Declaration," communicating worry over EDCs and approaching the European Commission (EC) to improve its administrative system overseeing these chemicals.^[23-24] In 2018, EC led a survey on cosmetic guideline "EC no. 1223/2009" in regards to the substances with endocrine properties, and the EC will soon publish its final report and assessment of discoveries from public and stakeholder meetings on current EU appraisal and the executives of endocrine disruptors.^[25] Instances of significant endocrine and metabolic disorders that occur due to ED's are given below with the number of population affected worldwide.

Diabetes

The rate of diabetes and related metabolic issues has significantly increased over the years and keeps increasing at a disturbing rate. In 2019 around 463 million grown-ups (20–79 years) were living with diabetes; by 2045, this will ascend to 700 million, as represented in Chart 1. Epidemiological and experimental proof propose a relationship between exposure to EDCs and type 2 diabetes mellitus (T2DM), particularly since the exposure to synthetic substances expanded hugely in the most recent decade, 374 million individuals are at an expanded danger of creating type 2 diabetes (T2D).^[26]

Obesity and Overweight

Obesity has been proposed to be one more unfriendly wellbeing impact of exposure to EDCs,^[27] during the

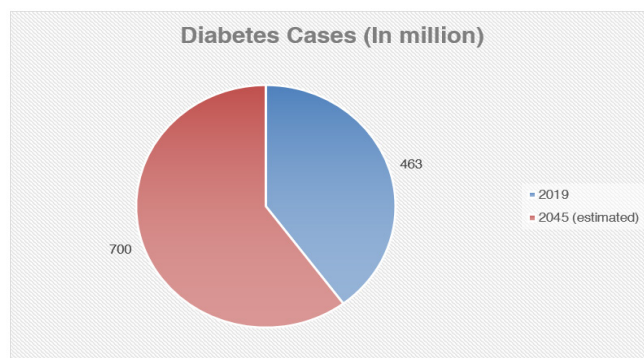


Chart 1: Diabetes Cases (in millions)^[26]

basic phases of advancement. Obesity is rapidly turning into a huge human wellbeing emergency. Overall obesity has almost significantly increased since 1975.^[28] In 2016, more than 1.9 billion grown-ups, 18 years and older, were overweight. Of these more, than 650 million were obese. More than 340 million kids and youths matured 5–19 were overweight or obese in 2016, and 38 million youngsters younger than five were overweight or fatty in 2019, as represented in Chart 2. The vast majority of the total populace lives in nations where overweight and obesity kill many individuals than underweight.^[29]

Historical Background of ED's

Generally, the term was formed in 1991 and was characterized by the "US Environmental Protection Agency (EPA) as an exogenous agent."^[30] Since 1940 there has been an outstanding expansion in the number of manufactured chemicals, some of which have been delivered into the climate. This substance transformation has irreversibly changed environments in a way that has a major impact on wildlife and human wellbeing. "Rachel Carson's book *Silent Spring*," published in 1962, was the first public alarming that natural contamination, specifically the pesticide DDT, may be liable for the diminished numbers of birds because of regenerative disappointment brought about by this and other harmful chemicals.^[31] The second advancement revelation was that of diethylstilbestrol (DES) given to pregnant ladies to deflect premature delivery. DES is comparable in its properties to natural estrogen chemicals. Two more unfortunate exposure examples are "Yusho in Japan (PCBs)," and "Yucheng in Taiwan (polychlorinated dibenzofurans)" in which polluted cooking oil caused mass harming. Of ongoing concern is the harming of schoolchildren in India in July 2013 through oil adulterated with the organophosphate pesticide monocrotophos, which brought about 23 deaths.^[32]

Endocrine Mechanisms of Action

Research has evidently demonstrated that EDCs can act at various destinations through various action mechanisms.^[33] A receptor-mediated mechanism has got the most consideration, yet the different modes of action (e.g., metabolism, transport, and hormone

synthesis) have been demonstrated to be similarly considerable.^[34–35] For most relationships announced between exposure to EDCs and diversity of biological results, the mechanism(s) of activity are inadequately perceived. This makes it hard to recognize immediate and aberrant impacts and essential versus optional impacts of exposure to EDCs. It likewise demonstrates that significant alert is essential in extrapolating from in vitro information to in vivo impacts, foreseeing impacts from restricted in vivo information, and extrapolating from trial information to human circumstance. An aggregate proof is fundamental in deciding under what conditions noticed impacts coming from exposure to EDCs happen due to endocrine-mediated mechanisms. EDCs can tie straightforwardly to receptors either as agonists or antagonists, so an increase or decrease in hormone effect occurs. However, there are different mechanisms of EDC activity portrayed, specifically with the inclusion of the AhR. The AhR is a ligand-activated transcription factor and a critical controller of the cell reaction to xenobiotic exposure.^[36]

Examples:

- *Bisphenol A (BPA)*: It is utilized to prepare polycarbonate plastics and epoxy resins, which are used in the manufacturing of various plastic substances and containers used for food storage.
- *Dioxins*: Resulted as a by-product from bleaching of paper and production of herbicide, due to burning of waste and wildfires, they get released into the environment.
- *Perchlorate*: It is an aerospace, weapon, and pharmaceutical industries by-product, generally present in fireworks and drinking water.^[37]

Individuals may come in contact with EDs through applied pesticide, cosmetic utilization, food, and beverages consumed. However, air, water, diet, and skin also play an important role in exposure to EDs.^[34]

Organization for Economic Co-operation and Development (OECD)

In the late 1990s, OECD nations chose to make a move to create methods to detect EDs. Because of scientific works and research effort, OECD began to research, test techniques that could be normalized and utilized in the regulation of EDs to identify and evaluate risks presented by EDs.^[38]

The OECD publishes the "Amended Guidance Document on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disruption." In 2012 and refreshed in 2018, it gives direction to assessing chemicals for ED.

The work on EDs testing and evaluation is administered by the "Working group of National Coordinators of the test guidelines program (WNT)" and overseen by four primary experts or advisory committee. Because of the versatile nature of the endocrine system, nonappearance

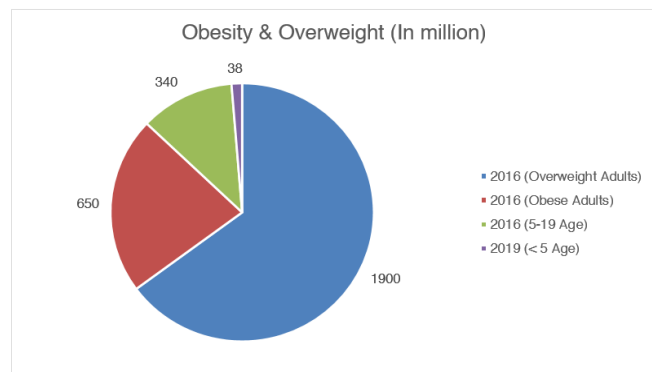


Chart 2: Obesity & Overweight (In millions) ^[29]



of a solitary technique equipped for recognizing endocrine disruption,^[39] so the efforts of the OECD have along these lines focused on the approval of explicit screening and testing guidelines.^[40]

Regulatory Perspectives of Endocrine Disruptor

As administrative programs assess products for their EDC properties, careful examination plan and information understanding are required to recognize reactions that are really resulted by endocrine and those that are not resulted by endocrine. It is especially significant in administrative conditions where measures are being worked to enable hazard-based guideline. Different agencies are in the cycle of setting up the projects and strategies to enable the access and safety part of presently utilized chemicals with close association with the endocrine framework, bringing about possible effects on generation, development, or potential improvement. Cautious may catch many general mechanisms that would not specifically denote an ED. Various regulated and emerging countries working on the testing and regulatory evaluation of endocrine disruptors are discussed in this article.^[41]

USA

Various US government offices manage Chemical-containing substances. Both the "US EPA" and the "Food and Drug Administration (FDA)" implement laws to assure chemical and substances are safe for purchaser use. Since their foundation, both the EPA and FDA have formed enormous steps in the laws ensuring purchasers against unsafe substances, for example, the 1976 "Toxic Substances Control Act (TSCA)" and the 1938 "Federal Food, Drug, and Cosmetic (FDC) Act."^[42]

Once in a while, the impacts of endocrine ED substances in customer items aren't found until long after they've been available. A perfect representation of this is DES, a kind of engineered estrogen recommended between 1938 and 1971 to stop pregnancy complications. It wasn't until 15-20 years after moms consumed DES that the unsafe results surfaced when their girls started building up an uncommon disease called clear cell adenocarcinoma (CCA) early in their lives.^[43-44]

The EPA starts screening, testing, and examination projects to collect data the agency uses to assess conceivable endocrine impacts related to the utilization of a substance. EPA finds a way to alleviate any harm related to the safety of public wellbeing and the environment.^[45]

Endocrine Disruptor Screening Program (EDSP)

Two-layered testing methodology (estrogen, androgen, and thyroid hormonal frameworks, and wildlife) Tier 1: recognizable proof and grouping of possible EDCs by in-vitro and in-vivo examines; "Series 890"-EDSP Test Guidelines Tier 2: Associations between concentration and response in animal models fixation reaction connections in creature models.^[46]

The EDKB information base at present contains 3,257 records of more than 1,800 EDs from various measures, including binding of estrogen and androgen receptor, androgen receptor, heterotropic movement, cell expansion, and gene assay of the receptor. For example, data for each compound, chemical structure, type of assay, potency, and so on are coordinated to enable proficient detection. An easy to use interface gives fast navigation, Boolean inquiries on EDs.^[47]

EUROPE

There is developing worry in the EU and worldwide about negative human wellbeing and ecological effects, perhaps brought about by endocrine disruptors.^[48] The EU has presented explicit administrative commitments pointed toward eliminating endocrine disruptors in water, industrial chemicals, and biocides. On 7 November 2018, the Commission has received a Communication affirming its obligation to shielding residents and the climate from unsafe chemicals.

The "European Commission (EC)" has a Strategy on EDs since 1999. Resulting updates to EU enactment on chemical products considered this strategy. The seventh "Environment Action Program (EAP)," received in 2013 by the European Parliament and the Council, accommodates the harmonization of hazard-based models for the distinguishing identification of EDs. The "Plant Protection Products Regulation (EC) 1107/2009 and the Biocidal Products Regulation (EU) 528/2012" gives the foundation of logical criteria to find the substances with disturbing endocrine characteristics. Extra administrative arrangements for EDs are covered under REACH.28 The EC published a chemical system for manageability on 14 October 2020. It is important for the EU's zero contamination aspiration, which is a critical responsibility of the "European Green Deal." In the previous many years, science on ED has progressed altogether and progress has been accounted in scientific publications by the EC and by EU organizations, in particular the Joint Research Center (JRC), the European Food Safety Authority (EFSA), and the European Chemicals Agency (ECHA).^[49-50]

JAPAN

Japan has been among the main countries to convey the impact of ED on a public level. In 1997 the Environmental Agency of Japan started an "Exogenous Endocrine Disrupting Chemical Task Force" under "Tsuguyoshi Suzuki," which expected to gather, organize, and review logical data accessible on the event of ED.^[51] Japan has been dynamic in exploring EDs for 10 years. In 1998, the "Ministry of Environment Protection (MEP)" began Strategic Programs on Environmental Endocrine Disruptors (SPEED)" with attention to screening of natural EDs. Under the program, authorities organized 67

presumed EDs for additional examination. In November 2000 authorities updated the list down to 65 chemicals.

Japan MEP is currently driving another program named EXTEND (Extended Tasks on Endocrine Disruption) 2010, planning to quicken the foundation and execution of evaluation procedures toward the objective to appropriately survey the environmental danger of endocrine-disrupting impacts of chemical products and to look in the administrative measures if needed.^[52] Based on these projects, observations were begun all through Japan to decide the degree of environmental contamination and its consequences for wildlife. Other Japanese governments, for example, "Ministry of Health and Welfare (MHW), Ministry of Agriculture, Forestry and Fisheries (MAFF), Ministry of Construction (MOC)," and nearby governments additionally began concentrates on this subject.^[53]

CHINA

China's quick economic development, chemical-related ecological issues have gotten progressively important, and the environmental administration of chemicals has collected expanded consideration from the government.^[54] Yet there is no committed guideline for EDs in China. "The Ministry of Environmental Protection (MOEP) and the Ministry of Agriculture (MOA)" are starting to lead the projects for controlling EDs inside their jurisdictions.^[55] In Dec 2015, the Ministry of Agriculture declared the publication of industry-standard "NY/T2873-2015 Evaluation Method of the Endocrine Disruption Effects of Pesticides." The standard was executed from 1 April 2016.

NY/T2873-2015 comprises 7 testing strategies given in two levels (in vitro and in vivo). They can be utilized to screen, whether a pesticide is ED or not. The strategies are like the strategies created by US EPA.^[56]

The "Chinese Ministry of Ecology and Environment (MEE)," earlier the Ministry of Environmental Protection (MEP), gave the "Measures on the Environmental Management of New Chemical Substances" (MEE Order No. 12) on April 29, 2020, which will take the place of the current MEP Order No. 7 on January 1, 2021. To execute MEE Order No. 12, the MEE delivered the "Direction for Environmental Management Registration of New Chemical Substances (Draft for Consultation)" (Draft Guidance) on August 17, 2020, to take the place of the current "Direction for New Chemical Substances Notification and Registration" in actuality under MEP Order No. 7 since October 15, 2010. The cutoff time to submit remarks to MEE for the Draft Guidance is September 6, 2020. The Draft Guidance gives a few insights concerning the new chemical product notice and enrollment under MEE Order No. 12. The important issues in the Draft Guidance are summed up below:

- The draft guidance determines that the active pharmaceutical and pesticide components are kept

out from the extent of the new chemical products substance notification and enrollment.

- As in "MEE Order No. 12," the Draft Guidance does not keep the low volume exclusion for new chemical products utilized for research with yearly manufacturing or import volumes of under 100 kilograms (kg).
- The Draft Guidance indicates that worldwide research centers used to perform physicochemical properties testing must give according to "International Organization for Standardization (ISO) 17025 or Good Laboratory Practices (GLP)" and the worldwide toxicology and ecotoxicology testing labs should be in consistence with GLPs.
- Based on the Draft Guidance, the protection period of 5-years for confidential data on the detection of new chemical products could be expanded if the products don't have any natural or health adverse classification.
- Three genotoxicity tests, incorporating an in vivo genotoxicity test, must be done for regular enrollment whatever the test consequences of the in vitro genotoxicity tests.
- The important new use enlistment is considered as a standard enrollment with similar methodology and information requirements as regular registration.^[57]

BRAZIL

In Brazil, EDCs are expressed with regards to the administrative structure on pesticides and in the policy, activity to set up a public enactment on industrial chemicals.^[58] The Brazilian administrative system on pesticides comprises of the "Federal Law 7802/1989" and the "Decree 4074/2002." It sets arrangements for pesticides and their segments in Brazil, including rules for their manufacturing, import, labeling, packaging, use, and disposal. The Brazilian administrative structure on pesticides doesn't express any legal measures for the Identification of EDCs. The toxicological evaluation of potential endocrine disturbing effects of a pesticide is executed according to the situation utilizing a weight of evidence methodology. In Oct 2018, the "National Chemicals Safety Commission (Comitê Nacional Sobre Segurança Química, or CONASQ), alongside the Ministry of Environment (Ministério do Meio Ambiente, or MME)," published a Preliminary Bill for the Evaluation, Inventory, and Control of Chemical Products.

National Inventory of Chemical Substances

Article 6 and 7 of the draft law needs that importers or the manufacturer of industrial chemical products, together with substances for mixtures, in case of a sum equivalent to or more than 1 ton for every year (depends upon an average of 3 years), present the following data to the National Register of Chemical Substances kept up by CONASQ. All substances collected will be utilized to



construct the National Inventory of Chemical Substances in Brazil.

- Company recognition proof of importers or manufacturer;
- Product detection, for example, CAS name or IUPAC name and CAS number if accessible.
- Quantity yielded or imported every year
- Suggested uses

It is assumed that the cutoff time for submitting the above data will be 3 years from the accessibility of a substance.

New Substance Registration

When the national existing chemical product inventory has been settled, chemical products that are not recorded will be viewed as new chemical products. Importers and manufacturers of new chemical products need to enroll those new products by presenting extra investigations and risk evaluation reports. Information prerequisites will increment with tonnage bands.

Evaluation

New products and certain current industrial chemical on the inventory will be chosen for risk assessment by "Industrial Chemicals Assessment Technical Committee" if they meet the following measures:

- Persistent, bio-aggregate, or hazard to the climate
- Mutagenic, Carcinogenic, and harmful to reproduction
- EDs depends on scientific evidence
- There are significant expected exposure to people and the climate;
- Controlled by global conventions of which Brazil is a part or signatory.

Manufacturers and importers of industrial chemicals, subject to assessment, will be needed to present certain data, studies, and safety information sheets to CONASQ to help hazard evaluation. Depends upon the effects of risk evaluation, CONASQ may stop or limit the import, manufacturing, exchange, or utilization of certain chemical products.^[59-60]

AUSTRALIA

The reviews can inform recognizable proof of the likely resources of EDCs in Australian conditions of WWTPs which have been conducted in a few nations. These overviews have announced the occurrence of some EDCs in WWTP effluents and their accepting surroundings, even though there is a scarcity of data identifying the presence of EDCs in the Australian riverine climate. Evaluation of endocrine disturbance in freshwater frameworks has been attempted partly in Australia, even though various examinations have discovered proof of ED in the marine climate because of human effects.^[61-62] However, less work done in Australia would propose that various EDCs are available in freshwater frameworks in metropolitan, peri-metropolitan and rural territories. In Australia, the impacts of EDCs on the behavior of certain fish species

in the Sydney basin have been shown by Dr. Richard Lim, associates, and others.^[63-64] The presence of EDCs is both confirmed by analytical procedures focusing on specific substances and biological examines evaluating the general ED potential (usually as estrogenic action) of water samples. Responsibility regarding the guideline of chemicals substances in Australia is divided among the Australian government and the states and domains. However, the Australian government takes liability for managing the introduction (for example, importation) of chemicals, while states and domains manage their utilization and removal. Further, unique government offices have a part in substance guidelines relying upon the utilization of the compound (for example, remedial use, agricultural and veterinary use, use in food, and so on).

The Department of Health controls the entry of industrial chemicals through the "National Industrial Chemicals Notification and Assessment Scheme (NICNAS)." NICNAS has published risk evaluations of chemicals that can cause unfavorable developmental impacts via acting on the endocrine framework. These incorporate certain of the phthalates NICNAS has surveyed and a subclass of brominated fire retardants, which indirectly affect thyroid hormone levels. For every one of these chemicals, the impacts are dose-responsive.^[65]

SOUTH AFRICA

South Africa (SA) has encountered quick industrial and metropolitan development, particularly in the expansion in the number of small enterprises. SA is known to have utilized and abused most chemicals compounds recorded by developed and developing nations as EDs.^[66] The presence of EDCs has been reported in the SA climate, which consequently uncovered people and natural life to conceivable health problems.^[67] Many water bodies in the nation get critical contributions of common and engineered chemical products, which sometimes act as EDCs, hence establishing a danger to the reproduction process of oceanic creatures.^[68]

As an arising global economy relying largely upon horticulture, chemical companies, and mining, South Africa actually faces difficulties in the area of appropriate garbage removal from various industrial and rural sources, water, silt, and serum tests affirmed the presence of EDCs. This weight of proof collected on EDCs in the SA climate has represented an enormous challenge in water resources administration. The critical concentration of phthalates have been described in some environmental samples in the country.^[69]

Territories of considerable importance have been dismissed in checking EDCs in the SA climate (e.g. Municipal treated wastewater, landfill sites). Although wastewaters from households and companies are generally treated before they are delivered into the

waterway system, examines have indicated that they frequently contain EDCs.

South Africa turned into the primary African nation to manage a substance as an EDC when it stops the import, manufacturing, export, and sale of the newborn child feeding bottles incorporating BPA in 2011 (Government of South Africa 2011). The next year, at the "Third International Conference on Chemicals Management (ICCM3)" in Nairobi, the whole African region finalized an agreement of greater than 100 nations to assign EDCs as a worldwide arising strategy issue (SAICM 2012). In 2013, African representatives gave a brief layout of administrative requirements for EDCs in an agreement goal adopted at the fifth regional gathering of the "Strategic Approach to International Chemicals Management (SAICM)" in Pretoria (SAICM 2014). The goal perceived the shortage of data on EDCs found in human and wildlife tissues in Africa;

The requirement for activities identified with EDCs communicated by African government controllers was strengthened in 2015 at the "Fourth International Conference on Chemicals Management (ICCM4)." A goal on EDCs by greater than 100 governments approached UNEP and WHO to address the necessities identified by developing nations.^[70]

INDIA

India delivered the fourth draft Chemicals (Management and Safety) Rules on March 16, 2020. The "Bureau of Indian Standards (BIS)" has revised the norms for infant feeding bottles in 2015 according to IS 14625:2015 and denied the utilization of BPA in child feeding containers. India incorporated in the draft rules the foundation of a steering committee that "will direct technical and organization matters emerging out of these rules, and carry out the responsibilities that might be assigned to it under these Rules." A Scientific Committee and a Risk Assessment Committee would be created. A "Chemical Regulatory Division (the Division)" will be set up and answerable for planning with the Committees and offering specialized help to the boards. The Division, like ECHA, would be liable for the assessment of notice and enrollments and give proposals to the Committees.^[71]

The first notification would start one year from the Rules coming into power and would end 180 days from the beginning. Notice is needed for all current products imported or made at or over one metric ton every year. All new products should be notified in any event 90 days before the date they are placed in India. Schedule V gives the data needed for the notification. The data is like the necessities determined in the pre-registration period of South Korea's 2019 revised Act on Registration and Evaluation of Chemicals (K-REACH) and incorporates considerable demonstration of product identification, use, and hazard characterization detail.^[72]

BANGLADESH

Developed or industrialized nations are performing progressed EDCs related examinations where non-industrial nations are getting aware of EDCs in the present. Understanding the danger of EDCs to kids and future generations, "Environment and Social Development Organization-ESDO" from Bangladesh alongside IPEN uphold the selection of EDCs an arising worldwide approach issue under SAICM and the SAICM partners activity to organized EDCs.

Initiatives and Regulations in Bangladesh

There is a small exploration done on the EDCs, and there is even a hole in the information about the historical pattern of EDCs, for example, because of the absence of information, it couldn't be affirmed if EDCs are liable for expanded reproductive issues. Considering the circumstance, ESDO has just begun an examination to survey the nation's circumstances on EDCs and their effect on climate and human wellbeing. ESDO started public awareness seminar on EDCs at the end of 2013.

Considering the dangers which have been called attention to by researchers, the administrative improvement to confine the utilization of EDCs in customer items has been fairly delayed in Bangladesh. The "Essential Commodity Act, 1990" should implicate on EDCs. The resolution behind the implementation of this act is to incorporate a wide range of exercises like storage, transport, distribution, removal, obtaining, use, or utilization of any essential item containing manufactured chemicals.^[73]

KOREA

In the Korean administrative systems, EDCs are expressly tended to in the act on the "Registration and Evaluation of Chemicals (K-REACH)." The guideline went into power on January first, 2015, and sets regulations on the enlistment and evaluation of synthetics on the Korean market. It likewise incorporates administrative instruments for the management of potential danger presented by these synthetics. It is regulated by the Korean Ministry of Environment (MoE).

K-REACH expresses EDC: Article 25(1) states that substances that cause or are probably going to cause disturbing endocrine impacts might be assigned as substances subject to approval. A substance concern to approval requires consent by the MoE before its produced, import, or use. Moreover, any substance that is beginning to represent a danger isn't assigned as a substance subject to approval can likewise be regulated by a limitation or dependent upon prohibition. Registration and assessment of chemical substances under K-REACH are described in Fig. 1.^[74]

MALAYSIA

EDC study in Malaysia is new and started to be seriously just since 1999. The Ministry of Health has just begun to



take note of the presence of EDC's and conceded some funding for EDC research in the country. The Ministry of Agriculture had started to investigate the EDC viewpoint. The United Nations University, along with Shimadzu

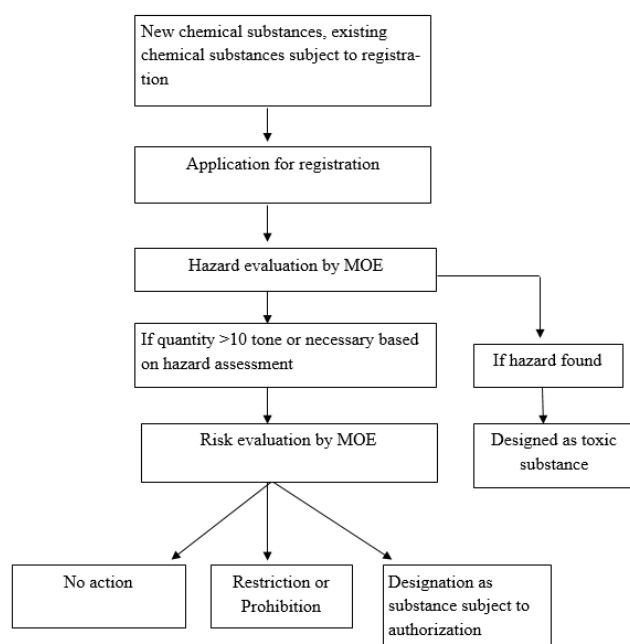


Fig. 1: Registration and assessment of chemical substances under K-REACH described.^[74]

Corporation, has started and effectively directed a task for five years. During the most recent three years, the exploration was on EDC.

One significant investigation that led in Malaysia is the observation of phytoestrogens in the blood of the Malaysian peoples. Some Animal examinations were also led by feeding the animal with a few presumed EDC's, such as sorbic acid, glyphosate, and phthalates. A few measures of the fed animal were seen following after 2 and 6 weeks. The measures incorporate the body's weight, the weight of the liver, testis weight, and testosterone levels. There are some significant outcomes here. Glyphosate, lindane, caused a slight decrease in the testis weight after the following 6 weeks.

The authorities have looked at the requirement to increase the research in EDC's. There are already authorities involved in Malaysia for observation of EDC's, and the Malaysian scientists are ready to cooperate further with overseas agencies and institutions.^[75]

Comparison of Endocrine Disruptor's Regulations

Every regulatory agency has a unique process to deal with the impact and approval of the endocrine disruptors. This process of approval is based on various factors like the type of application submission, review timeline, and so on. The similarities and differences for various regulatory aspects of endocrine disruptors enlisted in Table 1 and 2.^[76-77]

Table 1: Difference between the regulatory environments of emerging countries: ^[55-59-74-71-75-77]

	China	Brazil	Australia	South Africa	India	Bangladesh	Korea	Malaysia
Regulatory authority	Ministry of Environment and Ministry of Agriculture	Nationtional chemicals safety commission and Ministry of Health	Australia government and states, Department of Health	Government of SA	Steering Committee, Scientific and Risk Assessment Committee	Environment and social development organization	Korean Ministry of Environment	Ministry of Health, Ministry of Agriculture
Dossier submission	No	No	No	No	No	No	No	No
WHO member	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OECD member	No	No	Yes	No	No	No	Yes	No
ED evaluation pathways	Yes	Yes	Yes	No	No	Yes	Yes	No
Time frame for evaluation	No	No	No	No	No	No	No	No
language	Chinese	Portuguese/ English	English	English	English	English	Korean/ English	Malay/ English
Decision making organization for ED	Ministry of Environment and Ministry of Agriculture	Nationtional chemicals safety commission and Ministry of Health	Australia government and states	Government of SA	Steering Committee	Environment and social development organization	Korean Ministry of Environment	Ministry of Health, Ministry of Agriculture

Table 2: Difference between regulatory environments of regulated countries^[42-49-55-77]

	USA	Europe	Japan
Regulatory authority	US Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA)	European Commission, Joint Research Centre (JRC), European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA).	Ministry of Environment Protection
Dossier submission	No	No	No
WHO member	No	Yes	Yes
OECD member	Yes	Yes	Yes
ED evaluation pathways	Yes	Yes	Yes
Time frame for evaluation	No	No	No
language	English	English	English/Japanese
Decision making organization for ED	US Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA)	European Commission	Exogenous Endocrine Disrupting Chemical Task Force

CONCLUSION

In this article, we've put our best effort to recapitulate the current state-of-the-art regulatory framework and scientific approaches in light of EDCs and make out issues and future needs about the current shortcomings in this field. The highlight about regulated USA, Europe, Australia, and Japan) and emerging markets (China, Brazil, South Africa, India, Bangladesh, Korea, and Malaysia). The regulated market like Europe is highly aware of the impact of EDs on human and animal health, and the USA and Japan follow it; regulated countries implement several regulations to control and evaluate the endocrine disruptors. In emerging countries like China, India, Korea, etc. regulations related to EDs are in the infancy stage. Still, they are doing well through various projects and researches on an individual basis. In collaboration with various international organizations like WHO, the OECD, because of the high adverse impact of EDs on health and the environment, the world needs to develop a strongly regulated environment for EDs.

REFERENCES

- Lauretta R, Sansone A, Sansone M, Romanelli F, Romanelli F. Endocrine disrupting chemicals: effects on endocrine glands. *Front Endocrinol.* 2019; 10:178.
- <https://hospital.uillinois.edu/primary-and-specialty-care/diabetes-and-endocrinology/endocrine-disorders> [Last accessed on 2 Dec 2020].
- https://www.physipedia.com/Metabolic/Endocrine_Disorders [Last accessed on 3 Dec 2020].
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev.* 2009; 30(4):293-342.
- <https://www.epa.gov/endocrine-disruption/what-endocrine-disruption> [Last accessed on 13 Dec 2020].
- <https://www.hormone.org/your-health-and-hormones/endocrine-disrupting-chemicals-edcs> [Last accessed on 10 Dec 2020].
- https://ec.europa.eu/environment/chemicals/endocrine/index_en.htm [Last accessed on 13 Dec 2020].
- <https://www.msmanuals.com/home/hormonal-and-metabolic-disorders/biology-of-the-endocrine-system/endocrine-disorders> [Last accessed on 5 Dec 2020].
- <https://www.msmanuals.com/home/hormonal-and-metabolic-disorders/biology-of-the-endocrine-system/endocrine-disorders> [Last accessed on 5 Dec 2020].
- Ricci PF. Endocrine disruptors: improving regulatory science policy. *Dose-Response.* 2015 ;13(4).
- Dhiman SK, Dureja H. Significance of and Challenges in Regulating Endocrine Disruptors-How Regulators and Industry Can Conquer?. *ENDOCR METAB IMMUNE Disorders-Drug Targets.* 2020;20(10):1664-81.
- Kassotis CD, Vandenberg LN, Demeneix BA, Porta M, Slama R, Trasande L. Endocrine disrupting chemicals: economic, regulatory, and policy implications. *The Lancet Diabetes Endocrinol.* 2020; 8(8):719-730.
- Damstra T, Barlow S, Bergman A, Kavlock R, Van KG. Global assessment of the state-of-the-science of endocrine disruptors. Geneva: World Health Organization. 2002:11-32.
- Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol.* 2015; 40(1):241-258.
- <https://www.verywellhealth.com/endocrine-disruptors-and-role-in-cancer-4781570> [Last accessed on 9 Dec 2020].
- Casals CC, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. *Annu Rev Physiol.* 2011; 73:135-162.
- Legler J, Brouwer A. Are brominated flame retardants endocrine disruptors?. *Environ Int.* 2003; 29(6):879-885.
- Bigsby R, Chapin RE, Daston GP, Davis BJ, Gorski J, Gray LE, Howdeshell KL, Zoeller RT, Vom Saal FS. Evaluating the effects of endocrine disruptors on endocrine function during development. *Environ. Health Perspect.* 1999; 107(4):613-8.
- Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect.* 2003; 111(4):389-394.
- http://www.schwartzdiabetesdoc.com/newsletters-2014/2014-Endocrine_Disrupting_Chemicals.doc [Last accessed on 15 Dec 2020].
- <https://www.statista.com/statistics/302081/revenue-of-global-chemical-industry/> [Last accessed on 15 Dec 2020].
- Gore AC, Crews D, Doan LL, La MM, Patisaul H, Zota A. Introduction to endocrine disrupting chemicals (EDCs). A guide for public interest organizations and policy-makers. In *Endocr Soc.* 2014; 21-2:1-69.
- [http://www.collegiumramazzini.org/download/EDCs_Recommendations\(2013\).pdf](http://www.collegiumramazzini.org/download/EDCs_Recommendations(2013).pdf) ccc. [Last accessed on 15 Dec 2020].
- http://www.brunel.ac.uk/_data/assets/pdf_file/0005/300200/The_Berlaymont_Declaration_on_Endocrine_Disrupters.pdf [Last accessed on 18 Dec 2020].



25. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_233.pdf [Last accessed on 18 Dec 2020].
26. <https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html> [Last accessed on 5 Dec 2020].
27. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. *Nat Rev Endocrinol*. 2015; 11(11):653-661.
28. Newbold RR, Padilla BE, Jefferson WN, Heindel JJ. Effects of endocrine disruptors on obesity. *Int J Andrology*. 2008; 31(2):201-208.
29. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> [Last accessed on 7 Dec 2020].
30. Diamanti KE, Palioura E, Kandarakis SA. The impact of endocrine disruptors on endocrine targets. *Horm Metab Res*. 2010; 42(08): 543-552.
31. Darbre PD. The history of endocrine-disrupting chemicals. *Current Opinion in Endocr Metab Res*. 2019; 7:26-33.
32. Flaws J, Dandimopoulou P, Patisaul HB. PLASTICS, EDCs & HEALTH
33. Crews D, Willingham E, Skipper JK. Endocrine disruptors: present issues, future directions. *Q Rev Biol*. 2000; 75(3):243-260.
34. Aylward LL, Goodman JE, Charnley G, Rhomberg LR. A margin-of-exposure approach to assessment of noncancer risks of dioxins based on human exposure and response data. *Environ Health Perspect*. 2008; 116(10):1344-1351.
35. Kiyama R, Wada KY. Estrogenic endocrine disruptors: Molecular mechanisms of action. *Environ Int*. 2015; 83:11-40.
36. Swedenborg E, Rügge J, Mäkelä S, Pongratz I. Endocrine disruptive chemicals: mechanisms of action and involvement in metabolic disorders. *J Mol Endocrinol*. 2009; 43(1):1-10.
37. Canadian center for occupational health and safety fact sheet and information of endocrine disruptors. <https://www.ccohs.ca/oshanswers/chemicals/endocrine.html>. Accessed 18 December 2020.
38. Huet MC. OECD activity on endocrine disrupters test guidelines development. *Ecotoxicology*. 2000; 9(1):77-84.
39. Browne P, Van WL. Gourmelon A. OECD approaches and considerations for regulatory evaluation of endocrine disruptors. *Mol. Cellular Endocrinol*. 2020; 504:110675.
40. Gelbke HP, Kayser M, Poole A. OECD test strategies and methods for endocrine disruptors. *Toxicol*. 2004; 205(1-2):17-25.
41. Ashby J, Houthoff E, Kennedy SJ, Stevens J, Bars R, Jekat FW, Cambell P, Van MJ, Carpanini FM, Randall GL. The challenge posed by endocrine-disrupting chemicals. *Environ Health Perspect*. 1997; 105(2):164-169.
42. <https://www.alpco.com/regulating-endocrine-disrupting-chemicals-consumer-products> [Last accessed on 18 Dec 2020].
43. <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2013/9/fda-outlines-endocrine-disruptor-testing-approach-citing-historical-data> [Last accessed on 20 Dec 2020].
44. https://www.schc.org/assets/meetings/spring_2016/posters/duft-schimera-ramisch.pdf [Last accessed on 21 Dec 2020].
45. <https://www.epa.gov/endocrine-disruption> [Last accessed on 21 Dec 2020].
46. Browne P, Noyes PD, Casey WM, Dix DJ. Application of adverse outcome pathways to US EPA's endocrine disruptor screening program. *Environ Health Perspect*. 2017; 125(9):096001.
47. Ding D, Xu L, Fang H, Hong H, Perkins R, Harris S, Bearden ED, Shi L, Tong W. The EDKB: an established knowledge base for endocrine disrupting chemicals. *BMC Bioinform*. 2010; 11:1-7.
48. European Union framework on endocrine disruptors and commission communication on EDs. https://ec.europa.eu/info/policies/endocrine-disruptors_en [Last accessed on 23 Dec 2020].
49. https://ec.europa.eu/environment/chemicals/endocrine/index_en.htm [Last accessed on 23 Dec 2020].
50. https://ec.europa.eu/health/endocrine_disruptors/overview_en [Last accessed on 25 Dec 2020].
51. Nakata K. Endocrine disruptors and environmental impact in Japan. *Cad Saúde Pública*. 2002; 18:531-548.
52. https://www.chemsafetypro.com/Topics/Japan/Endocrine_Disruptors_Regulations_and_Lists_in_Japan.html [Last accessed on 27 Dec 2020].
53. Hecker M, Hollert H. Endocrine disruptor screening: regulatory perspectives and needs. *Environ Sci Eur*. 2011; 23(1):1-4.
54. Wang H, Yan ZG, Li H, Yang NY, Leung KM, Wang YZ, Yu RZ, Zhang L, Wang WH, Jiao CY, Liu ZT. Progress of environmental management and risk assessment of industrial chemicals in China. *Environ Pollut*. 2012;165:174-181.
55. <http://news.agropages.com/News/NewsDetail---19426.htm> [Last accessed on 23 Dec 2020].
56. https://www.chemsafetypro.com/Topics/China/Endocrine_Disruptors_Regulations_and_Lists_in_China.html [Last accessed on 27 Dec 2020].
57. <https://www.lawbc.com/regulatory-developments/entry/china-publishes-draft-guidance-for-environmental-management-registration-of>. Accessed 23 December 2020.
58. Waissmann W. Health surveillance and endocrine disruptors. *Cadernos de Saúde Pública*. 2002; 18(2):511-517.
59. https://www.chemsafetypro.com/Topics/Brazil/chemical_regulations_in_Brazil_and_developments.html [Last accessed on 28 Dec 2020].
60. https://wedocs.unep.org/bitstream/handle/20.500.11822/25636/edc_report3.pdf?sequence=1&isAllowed=y [Last accessed on 28 Dec 2020].
61. Nias DJ, McKillup SC, Edyvane KS. Imposen in *Lepsiella vinosa* from southern Australia. *Mar Pollut Bull*. 1993; 26(7):380-384.
62. Reitsemä TJ, Spickett JT. Imposen in *Morula granulata* as bioindicator of tributyltin (TBT) contamination in the Dampier Archipelago, Western Australia. *Mar Pollut Bull*. 1999; 39(1-12):280-284.
63. Batty J, Lim R. Morphological and reproductive characteristics of male mosquitofish (*Gambusia affinis holbrooki*) inhabiting sewage-contaminated waters in New South Wales, Australia. *Arch Environmental Contam Toxicol*. 1999; 36(3):301-307.
64. Doyle CJ, Lim RP. Sexual behavior and impregnation success of adult male mosquitofish following exposure to 17 β -estradiol. *Ecotox Environ Safe*. 2005; 61(3):392-397.
65. Leusch FD, Chapman HF, van den Heuvel MR, Tan BL, Gooneratne SR, Tremblay LA. Bioassay-derived androgenic and estrogenic activity in municipal sewage in Australia and New Zealand. *Ecotox Environ Safe*. 2006; 65(3):403-411.
66. Burger AE, Nel A. Scoping study to determine the potential impact of agricultural chemical substances (pesticides) with endocrine disruptor properties on the water resources of South Africa. Pretoria: Water Research Commission; 2008.
67. Bornman MS, Aneck-Hahn NH, De Jager C, Wagenaar GM, Bouwman H, Barnhoorn IE, Patrick SM, Vandenberg LN, Kortenkamp A, Blumberg B, Kimmins S. Endocrine disruptors and health effects in Africa: a call for action. *Environ Health Perspect*. 2017; 125(8):085005.
68. Burger AE, Moolman AP. First phase of an endocrine research programme for South African water systems. *Water Pract Technol*. 2006; 1(2).
69. Olujimi OO, Fatoki OS, Odendaal JP, Okonkwo JO. Endocrine disrupting chemicals (phenol and phthalates) in the South African environment: a need for more monitoring. *Water SA* 2010; 36(5).
70. http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S1816-79502010000500017 [Last accessed on 29 Dec 2020].
71. <https://www.toxicslink.org/?q=endocrine-disrupting-chemicals> [Last accessed on 31 Dec 2020].
72. <https://www.natlawreview.com/article/india-announces-fourth-draft-chemicals-management-and-safety-rules> [Last accessed on 31 Dec 2020].
73. <https://esdo.org/endocrine-disrupting-chemicals-edcs/> [Last accessed on 31 Dec 2020].
74. https://wedocs.unep.org/bitstream/handle/20.500.11822/25636/edc_report3.pdf?sequence=&isAllowed=y [Last accessed on 28 Dec 2020].
75. https://www.env.go.jp/chemi/end/sympo/2001/report/pdf/e/mohd_e.pdf EDC study in Malaysia is new and started to be seriously just since 1999 The United Nations University, along with Shimadzu Corporation [Last accessed on 2 Jan 2021].
76. <https://www.who.int/countries/> [Last accessed on 4 Jan 2020].
77. <https://www.oecd.org/about/document/list-oecd-member-countries.htm> [Last accessed on 4 Jan 2021].

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