Endocrine-Disrupting Chemicals: An Invisible Threat

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Abstract:

A large burden of communicable and non-communicable diseases is attributable to environmental risk factors. The World Health Organization (WHO) estimates that environmental factors are responsible for 24% of the global burden of disease and 23% of all deaths. Much of the environmental disease burden is due to contaminated water, poor sanitation, air pollution, and exposure to chemicals like endocrine-disrupting chemicals (EDCs). These are present in everyday products that we use, eat, and are surrounded by. Endocrine disruptors may exert adverse effects on hormone function and hence on human health. The challenges of keeping our environment safe for optimal health is a responsibility we must all bear.

Key words: Endocrine-Disrupting Chemicals (EDCs), Pesticides, Consumer Products, Industrial Waste Pollution, Environment, Multihormonal Disorders.

Introduction

In 1962, a bestselling book called 'Silent Spring' by Rachel Carson alerted the world about the impact of environmental issues on health.[1] This eye-opening publication and other research-based information led to three landmark milestones of the 21st century: the establishment of the Environmental Protection Agency (EPA, USA), the first Earth Day being observed in 1970, and a ban on the use of the insecticide dichlorodiphenyltrichloroethane (DDT).[2]

Worldwide, people realised that spraying chemicals to control insects can also kill birds, other animals, and harm humans. These chemicals travel not only through the environment but also down food chains.

One woman's crusade created a domino effect to identify various chemicals that exist in our everyday environment, often taken for granted as harmless but unfortunately extremely detrimental to health. My understanding of her book is that she implied that any rampant, unregulated use of these chemicals would usher in a spring where no birds would sing and where human health would be compromised. Hence, the book was aptly titled 'Silent Spring'.

While modernisation of our lives has improved our skills, standards of living, and productivity, we may not be aware of the threat that we potentially face in terms of health issues, specifically the many silently lurking endocrine problems caused by these not-so-innocuous chemicals in our environment—the endocrine-disrupting chemicals (EDC).

We need to be aware, learn and research ways to decrease the use of EDCs and find alternative methods to replace these substances.

Endocrine disruptors or EDCs are natural or man-made chemicals that mimic or interfere with the body's hormones, i.e., the endocrine system. Some chemicals fool the body into over-responding or responding at inappropriate times, while others block the effects of a hormone from certain receptors.[3] These chemicals are linked with many health problems in both animals and humans. They can cause harmful effects in the individual or even their progeny. EDCs are responsible for adverse health outcomes that can emerge over the entire human lifespan.

Based on their origin, endocrine disruptors can be categorised as industrial (e.g., polychlorinated biphenyls [PCBs] and dioxins), agricultural (e.g., pesticides), pharmaceutical (e.g., parabens), and residential (e.g., bisphenol A). In addition, heavy

metals including lead, mercury, cadmium, and arsenic can be considered endocrine disruptors.

Background

According to the Endocrine Society of USA, there are nearly 85,000 human-made chemicals in the world, and 1,000 or more of them could be endocrine disruptors, based on their unique properties.

In 2009 and later in 2015, the Endocrine Society analysed 1,800 studies on EDCs and published evidence-based scientific statements. Their evidence showed how EDCs disrupt our hormones and harm our health. Adverse effects are linked to reproductive disorders, obesity, diabetes, neurological problems, immune and thyroid disorders, osteoporosis, attention deficit disorders, and hormone-related cancers.[4,5]

Historical Lessons

Three unfortunate events happened in the 1960s, 1970s and 1984.

Pregnant women who received the drug thalidomide to alleviate nausea in the first trimester had a significant risk of giving birth to infants with limb malformations. This proved that the foetus was vulnerable to pharmaceuticals given to the mother and that the placental barrier could be crossed.

The second event was use of diethylstilbestrol (DES), given to pregnant women to prevent miscarriage. DES, similar to natural oestrogen hormones, caused girls exposed to it *in utero* to often develop reproductive tract malformations, and some developed rare reproductive cancers in adolescence that were normally only seen in postmenopausal women. Because of the long latency between foetal exposure and disease in adolescence, the connection to the mother's use of DES was not initially obvious. However, experimental work in mice exposed to DES *in utero* identified reproductive disorders in the offspring of both sexes as they matured to adulthood. This cause-and-effect relationship between foetal DES exposure, reproductive tract malformations, and reproductive tract cancer later in life, seen both in humans and mice, was compelling. DES can cause epigenetic changes, altering the way genes are turned on and off in the reproductive organs of mice. These findings provide a possible explanation for how endocrine disruptors affect fertility and reproduction.[6,7]

The Bhopal gas tragedy in 1984—an accidental leak from a pesticide plant—was one of the worst industrial disasters, resulting in thousands of deaths within hours and affecting over 2 lakh people in that city. Many problems such as miscarriage, stillbirth, and pulmonary, neurological, ophthalmologic, and other diseases occurred in people that were exposed to methyl isocyanate (MIC). Even twenty years after the Bhopal incident, menstrual abnormalities, premature menopause and chromosomal abnormalities remain common problems among Bhopal MIC-exposed women and their female offspring.[8,9]

Where are EDCs Found in our Environment?

EDCs are ubiquitous in the environment. They are found in the air we breathe, in human food, many consumer products (e.g., carpets, toys, electronics, and even hand sanitisers),[10] in rivers, landfills, pesticides used in farmlands, etc. In India, some industries dispose untreated waste water into drainage systems that flow into rivers. Dangerously high levels of metals such as lead, cadmium, nickel and zinc have been detected in the Yamuna River, which is a major supply of drinking water to the nation's capital.

How do EDCs Reach Our Body?

Human exposure to EDCs mainly occurs via ingestion, inhalation and dermal uptake.[11] Most EDCs are lipophilic and accumulate in the adipose tissue, giving them a very long half-life in the body. It is difficult to assess the full impact of human exposure to EDCs because adverse effects develop gradually and may only manifest later in life. The timing of exposure is crucial. Developing foetus and neonates are the most vulnerable to endocrine disruption. EDCs may interfere with synthesis, action, and metabolism of sex-steroid hormones, leading to developmental and fertility problems, infertility, and hormone-sensitive cancers in both women and men.[12]

Even low doses of EDCs can be unsafe. The body's normal endocrine functioning involves very minute changes in hormone levels, yet even these small changes can cause significant problems in everyday functioning of the body.[13]

EDCs in India

India's economic growth has taken a huge toll on the environment. Rapid industrialisation and urbanisation have led to many environmental and social challenges, such as increased greenhouse emissions, depletion of natural resources, and a rise in concentrations of various synthetic chemical contaminants in the atmosphere and water resources. A lack of access to healthcare in India makes the population more susceptible to EDC exposure. Open burning of dumped waste and crop residue is a major source of air pollution and the atmospheric emission of several EDCs all over India.

Expanding megacities further contribute to EDC pollution and human exposure by altering the food supply chain and causing a shift from traditional to modern and chemical-intensive food production and processing system in developing countries like India. Furthermore, the modern lifestyle in megacities directly exposes humans to EDCs including those present in consumer and personal care products and household products such as carpets, flooring, cleaning products, etc.[14-17]

Some Well-Known Endocrine Disruptors

Bisphenol-A (BPA)

BPA is found in plastics, e.g. material of shatterproof windows in high-rise buildings, eyewear, and everyday used water bottles that store juice, and sodas, as well as coatings of metal food cans and water supply pipes. Due to its hormone-like properties, BPA may bind to oestrogen receptors, affecting body weight and tumour formation. It binds to androgen receptors and impairs male reproductive function. It can also affect the brains of foetuses and infants, and influence children's behaviour. Once in the body, BPA can negatively affect thyroid, adipose tissue, liver and heart.[18-20]

2,3,7,8-tetrachlorod-ibenzo-dioxin (TCDD)/dioxin

TCDD/dioxin is formed from the burning of household waste and is also found in meat and dairy products. Dioxins are highly

toxic and can cause reproductive and developmental problems, interfere with hormones, and cause cancer.

Polychlorinated biphenyls (PCBs)

PCBs are persistent organic pollutants, with high toxicity. These are found in electric equipment's including switches, voltage regulators, fluorescent lights, cable insulation, building materials, paint, glues, etc. Consuming fish from contaminated lakes or rivers, drinking contaminated water or breathing air near hazardous waste sites can expose humans to PCBs. Their endocrine-disrupting effects involve thyroid and reproductive systems.

Diethylhexylphthalates (DEHP)

DEHP is used as a plasticiser in polyvinyl chloride (PVC). This chemical is used in consumer products such as toys, automotive components, furniture, shoes, fragrances and outdoor wear. Exposure to DEHP is associated with disruptions in steroid and thyroid signalling. It is also associated with developmental and reproductive health issues and even carcinogenicity.

Phthalates

Phthalates are chemicals found in most products that come into contact with plastics during production, packaging, or delivery, e.g., nail polish, shampoo, and cosmetics. Chronic exposure to phthalates adversely affects pregnancy outcomes, child growth and development, and the reproductive systems of young children and adolescents.

Essential oils

Some essential oils in personal care products have been suggested to cause prepubertal gynaecomastia and premature thelarche in children. Chemicals in lavender oil and tea tree oil are potential endocrine disruptors. Researchers found that persistent exposure to lavender oil products is associated with premature breast development in girls, and abnormal breast development in boys.[18] The industry and others have refuted these findings, but many studies have shown a link between these oils and enlarged breast tissue in prepubertal boys. This condition resolves once they stop using these products. This has been refuted by some studies too, but it remains a concern amongst parents and paediatricians. Hence, more research is need in this area.[21]

Cadmium and arsenic

Both cadmium and arsenic are also EDCs. They are found everywhere, from groundwater and water pipes to tobacco products, fertiliser, gasoline, and even batteries. They are absorbed via respiratory or gastrointestinal tract. Arsenic is also reported to impair the host response to H1N1, leading to pulmonary inflammation and increased mortality.

Triclosan

Triclosan, a known EDC, is an antimicrobial agent added to personal care products like soaps, shampoos, and toothpaste.

Mercury and heavy metals

Mercury, lead, arsenic and cadmium are heavy metals with EDC properties. A link has been established between them and cancers, thyroid and reproductive functions.

Minamata disease is methylmercury (MeHg) poisoning that occurred in humans who ingested fish contaminated with MeHg in wastewater from a chemical plant in Japan. Symptoms of this disease were sensory disturbances, ataxia, dysarthria, visual and auditory disturbances. Even the foetus was poisoned by MeHg when their mothers ingested contaminated fish.[22]

Soy plant-based products

Soy plant-based products have phytoestrogens, chemicals produced by plants that mimic oestrogen and have been regarded by some scientists to be an EDC, with effect on oestrogen receptors, thyroid and steroid biosynthesis.

Effects of EDCs on Health

Endocrine disruptors can influence the functionality of the endocrine system by changing the normal levels of hormones, by mimicking the functions of endogenous hormones, or by altering the production of hormones.[23]

EDC and diabetes

India is called the diabetes capital of the world due to an exponential increase in diabetes prevalence in the last few decades. Lifestyle factors, dietary habits, stress and an aging life span could be contributory. However, it is no coincidence that the global increase in diabetes is associated with a massive surge in industrial chemical output.

A large volume of data is available from preclinical studies implicating commonly used synthetic compounds in the pathogenesis of diabetes. EDCs have been shown to interact with almost all the steps of insulin homeostasis, starting from its synthesis to its signalling and action.[24,25]

Serum concentration of organic pollutants was found to be positively correlated with diabetes prevalence. Many animal studies have proved this. Mice exposed to BPA *in utero* resulted in impaired insulin secretion and glucose tolerance.[26,27]

EDCs could likely play a significant role in pathogenesis of diabetes and development of insulin resistance. They interfere with a maximal number of pathways of insulin homeostasis.

However, human data establishing causality is lacking globally. There is maximal data available from BPA and TCDD from USA. Their evaluation among Indians, especially with regards to disturbed glucose metabolism, insulin resistance and beta-cell function is almost non-existent. Hence, urgent research in this area is needed, especially in view of rampant diabetes prevalence in India.

EDC and gestational diabetes mellitus

Gestational diabetes mellitus (GDM) has increased dramatically in the past 20 years together with the obesity epidemic. This increase parallels the rising use of EDCs.[28] Although the association between BPA and type 2 diabetes has been repeatedly investigated in epidemiological and animal studies, there is a lack of studies examining EDCs and GDM. In fact, the impact of environmental toxins on perinatal health outcomes has largely been overlooked.

Recognising this research gap, the American College of Obstetricians and Gynecologists (ACOG) and International Federation of Gynaecology and Obstetrics (FIGO), along with scientists and clinicians, called for collective action to do research

in the consequences of exposure to toxic environmental agents on women's health. Evidence is emerging to suggest signalling molecules and EDCs are involved in control of micro ribonucleic acid (miRNA) expression in trophoblast cells.[29]

EDC and thyroid gland

Certain endocrine disruptors, including perchlorate and thiocyanate, have been found to affect iodine absorption by inhibiting the sodium-iodide symporter channel. This results in impaired biosynthesis of thyroid hormones.[30,31]

The common sources of perchlorate include explosives, airbags, fertilisers, and some food items (milk, egg, fruits, and vegetables). Cigarette smoke is a potent source of thiocyanate. A study involving pubertal participants has shown that exposures to perchlorate, thiocyanate, and nitrates caused a marked reduction in free thyroxine levels.[32,33]

Impact on pituitary gland

Many endocrine disruptors directly act on the diencephalic system by mimicking the functions of neurotransmitters. This subsequently affects the hypothalamus-pituitary-gonadal axis and induces a number of consequences, including delay in puberty onset and disruption of the circadian system.[34] Certain endocrine disruptors, such as oestrogenic chemicals, have been found to increase the synthesis and secretion of pituitary hormones, including prolactin and thyroid-stimulating hormone (TSH). This subsequently increases the risk of breast and thyroid cancers. In addition, there is evidence suggesting the role of oestrogenic chemicals in the development and progression of pituitary gland cancer.

Effect on adrenal gland

Blood flow and high amounts of fatty acids (lipophilic) make the adrenal gland a suitable target for endocrine disruptors. Studies investigating the effect of these chemicals on the hypothalamus-pituitary-adrenal axis have highlighted the possibility of disrupted steroid hormone synthesis and metabolism. Specifically, endocrine disruptors have been found to impair adrenal steroidogenesis by modulating the functions of aromatase, 5-α reductase, and hydroxysteroid dehydrogenases.[34]

EDCs and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterised by multiple endocrine disturbances. Its underlying causes, although uncertain, are likely both genetic and environmental. Recently, there has been interest in whether EDCs in the environment, particularly BPA, may contribute to the disorder.

In animal models, exposure to BPA during the perinatal period dramatically disrupts ovarian and reproductive function in females, often at doses similar to typical levels of human exposure.[35,36]

Future research should focus on translating the work in animal models into human studies and determining whether additional EDCs, beyond BPA, may be important to consider.

EDC and obesity

BPA also appears to have obesogenic properties, disrupting normal metabolic activity and increasing susceptibility to weight gain.

Many studies have linked EDC exposure to stimulation of adipogenesis and weight gain. Obesogens promote proliferation and storage of fat cells. These obesogens can be BPA, PCB, dioxins, etc. At a molecular level, these EDCs can interfere with nuclear transcription that control lipid flux and adipocyte proliferation.[37,38]

Impact on reproductive system

Since most of the endocrine disruptors are able to mimic sex hormones, the highest adverse impact has been observed on the reproductive system. By interfering with sex steroid hormones, endocrine disruptors can significantly affect foetal development. Among various disruptors, synthetic oestrogens, phytoestrogens, pesticides, plasticisers, and industrial chemicals exhibit strong anti-androgenic and weak oestrogenic properties.[39,40]

During the development of the ovaries in animals, endocrine disruptors have been found to interfere with follicle formation, meiosis, and vitality. During the early postnatal period, these chemicals may alter the genetic transcription of somatic cells, which in turn may delay the onset of puberty in animal models. Exposure to BPA during the perinatal period dramatically disrupts ovarian and reproductive function in females, often at doses similar to typical levels of human exposure.

Impact on bone mineral density

Certain per-and polyfluoroalkyl substances (PFAS) and phthalates may be associated with reduced bone mineral density in adolescent males. PFAS and phthalates activate peroxisome proliferator-activated receptor gamma (PPAR-γ), suppressing osteoblast formation and are androgen receptor antagonists that may inhibit androgen-mediated osteoblast genesis.[41]

EDC and cancer

Exposure to oestrogen and androgen mimicking EDCs can promote breast and prostate cancer growth and even interfere with hormonal cancer therapy.[42] Prenatal exposure to certain EDCs increases breast cancer risk.

EDC and other conditions

Attention-deficit and hyperactivity disorder (ADHD) is one of the most common childhood disorders, which can continue through adolescence and into adulthood. ADHD symptoms include difficulty staying focused, paying attention, and controlling behaviour. Researchers reported that ordinary exposure to certain phthalates, as found in urine samples, was associated with ADHD-related behaviours in adolescence. The drug DES may be linked to an increased chance of developing ADHD in the grandchildren of women who used it during pregnancy.[43,44]

Why Should We Care?

EDCs can harm every organ in your body. This danger starts in the womb and can be particularly dangerous to the developing foetus, infants, and children.

EDCs are everywhere. In food, toys, cosmetics, medicines, and plastics as well as throughout the environment. You and I are even likely to have EDCs in our bodies.

While scientific evidence linking EDCs to health effects is strong, regulations have not always kept up with the latest endocrine science, which continues to give us more insight into these substances.

By interfering with our hormones, EDCs prevent our interconnected hormone systems from functioning normally. This creates health problems. In fact, the data linking some EDCs to chronic disease is comparable in strength to the evidence that links tobacco smoking with lung cancer.

Lessons to be Learnt

In 1976, an explosion at a chemical manufacturing plant in Seveso, Italy, exposed residents to high levels of dioxins. Another tragic exposure occurred in 1968 in Yusho, Japan (PCBs) and in 1979 in Yucheng, Taiwan, where polychlorinated dibenzofurans-contaminated cooking oil caused mass poisoning. While associations between increased human chemical exposures and increased disease rates are suggestive, they do not 'prove' that the two are linked. However, data from cell-based studies and animal studies provides evidence supporting this link. Proving that a chemical contributes to a human disease would require exposing a group of humans and then observing the resulting disorder. Though this type of testing is done for pharmaceuticals, it would be unethical and impossible to test the impact of toxicants on humans in this way.[45-47]

A 2019 International Pollutants Elimination Network study (IPEN) looked at two sites in Indonesia where plastic waste was dumped, burned, or used as fuel. They sampled chicken eggs from the area and found the eggs contained PCBs, polybrominated diphenyl ethers (PBDEs), and PFAS, among other chemicals and very high levels of dioxins. An adult eating just one egg from the vicinity of one site would exceed the European Union (EU) safety level for daily dioxin intake by 70 times. The eggs contained 2,000 times higher levels of dioxins than the background levels found in supermarket eggs of the area. Dioxins are EDCs and cancer-causing chemicals that are produced when plastics are burned. They are among the most toxic chemicals known.[48]

Gaps in Rules and Regulation

Unlike harmful substances such as tobacco or asbestos, few regulations exist for the manufacturing and use of EDCs. Most industrial chemicals are not tested for endocrine-disrupting qualities before they reach the market.

As certain diseases have increased in recent years along with human's use of chemicals, many scientists connect the two events. They say that genetic changes do not occur fast enough to explain the growth of these diseases. Some of these conditions are part of the endocrine system, leading some scientists to conclude that EDCs are to be blamed.

There are many reasons why it's difficult to study endocrine disruption in humans. There are hundreds of substances suspected of being EDCs. These chemicals have very different properties. Testing them individually is a giant task.

In 2002, the WHO, United Nations Environment Program (UNEP) and International Labour Organization (ILO) published a consensus report on Global Assessment of Endocrine Disruptors. In 2009, the REACH Regulation (Registration, Evaluation, Authorization and Restriction of Chemicals) laid down the general EU framework applicable to chemicals. The overall aim of all EU legislation on chemicals is to achieve a high level of protection of human health.[49,50]

Precautions

Even if some health effects are not fully proven, taking precautions is wise. Be familiar with EDCs to which you and your family may be exposed. Try to avoid unnecessary exposure to EDC-containing consumer products. The following is a list of precautionary steps that one can take to minimise EDC exposures. These precautions are especially important for those pregnant or planning a family:

- Thoroughly wash fruits and vegetables before consuming them
- Don't microwave plastic food containers or use them for storing hot liquids
- Avoid plastic containers designated Recycle Numbers 3, 6, and 7
- Reduce consumption of canned and processed foods
- Use glass, porcelain, or stainless-steel containers, when possible, especially for hot food and drinks.
- If possible, purchase organic produce, meat, and dairy products.
- Replace older non-stick pans with newer ceramic-coated pans.
- Exercise and activity is important for overall health
- Avoid outdoor exercise when pollution levels are high
- Choose products such as cosmetics, toiletries labelled "Phthalate-Free", "BPA-Free", and "Paraben-Free"
- At home replace and safely discard old fluorescent bulbs, batteries, and deteriorating construction materials from older buildings
- Minimise burning wood or trash
- Plant trees, which filter out airborne gases and particulate matter
- Avoid plastic toys
- Use infant formula bottles and toys that are labelled "BPA-Free"

Conclusion

By interfering with hormones, EDCs prevent the endocrine systems from functioning normally.[51]

Since chemicals are everywhere in the world, we are constantly exposed to multiple chemicals simultaneously. That makes it difficult to isolate the effect of a single chemical.[52]

Although evidence linking EDCs to adverse health outcomes continues to grow, the cause-and-effect relationship is not yet fully understood. Generally, chronic high exposures pose the highest risk, however, a developing foetus or infant is more vulnerable to lower exposures.

A person's genetic predisposition to specific health conditions, as well as additional environmental risk factors can modify how a person is affected by EDCs.

Studies in animal models and observational data in humans have shown that artificial sweeteners can act as potential endocrine disruptors by modifying hormone levels, metabolism and reproductive functions.[53,54]

Estimates suggest that more than 24% of human diseases and disorders globally are attributable to environmental factors, which also play a role in 80% of the deadliest diseases, including cancer, heart disease, and others. EDCs in the environment may contribute to disorders with hormonal background such as diabetes, neurological disorders, reproductive disorders, inflammation, and compromised immune functioning.

In 2019, the first version of the Database of Endocrine Disrupting Chemicals and their Toxicity profiles (DEDuCT) was released, listing 686 EDCs from 1,796 articles. In 2020, the second version of DEDuCT was released, expanding the list to 792 potential EDCs from 2,218 articles.[55] This rapid escalation in published articles reflect the enormity of this subject and lessons one needs to learn, before it is too late.

I will end this review with words of wisdom from Rachel Carson:

"If we are going to live so intimately with these chemicals eating and drinking them, taking them into the very marrow of our bones - we had better know something about their nature and their power".

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