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Endocrine Disrupting Chemicals: A Challenge to Child Health

Endokrin Sistemi Bozan Kimyasallar: Çocuk Sağlığına Bir Tehdit

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Dear Editor,

Endocrine-disrupting Chemicals: Definition

The World Health Organization (WHO), defines endocrine disrupting chemicals (EDC) as substances that alter one or more functions of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub) populations (WHO, International Programme on Chemical Safety) (1). They are broadly classified as estrogenic, anti-estrogenic, anti-androgenic and thyroid hormone disrupting compounds (1). The toxic effects of in-utero exposure to thalidomide and diethylstilbestrol (DES) in the 1960s and 1970s furnished the earliest knowledge on the fragility of the developing fetus, and led to the framing of "fragile fetus" concept by Howard Ben to depict the vulnerability of the developing fetus on exposure to environmental chemicals with endocrine properties (2). Theo Colborn, a wildlife biologist and the author of "Our stolen future", made the first modern day observations on health effects of EDCs on wildlife and human population and inferred that endocrine changes affecting fetus in-utero may have effects on many future generations to come (3).

Endocrine Disrupting Chemicals are Ubiquitous

An approximate 800 chemicals are suspected to adversely affect hormone synthesis, hormone receptors, or hormone conversion (1,2,4). EDCs may be natural (phytoestrogens in plants or fungal estrogens), or manmade (3,5). Examples of natural EDCs include isoflavonoids in soybeans, legumes; ligananes in grains, fruits and vegetables and coumestans in clover, and alfalfa among others (3,5). The synthetic compounds have assorted applications in today's world as pesticides, flame retardants, plastic additives, active ingredients in pharmaceuticals, food additives and contaminants, plastics, textiles, construction materials, hormonal therapies, personal care products and cosmetics which may result in residues and contaminants in food and other products (3,5). DES, a synthetic estrogen prescribed for

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preventing miscarriage between the 1940s-1970s was one of the first established examples of EDCs when a cluster of a new rare form of cancer, vaginal clear cell adenocarcinoma was identified in adolescent daughters of women who had taken the drug during pregnancy. It was also determined to result in various other benign reproductive tract abnormalities in prenatally exposed males and females (2).

Exposure to Endocrine Disrupting Chemicals

Humans are exposed to EDCs via ingestion of food, dust and water, inhalation of gases and particles in the air and dermal uptake (3). EDCs are also transferred to a developing fetus, or infant by transplacental route and breast milk (3). EDCs mimic or antagonize the effects of endogenous hormones, disrupt the synthesis of endogenous hormones or their receptors, or may alter target cell sensitivity (6). The mechanisms by which EDCs affect developmental events are identified to be numerous and include changes in the neuro-endocrine system, epigenetic mechanisms and/or direct effects on gene expression (2).

Vulnerability of Children and Their Windows of Exposure

Children are at risk of higher exposures to these chemicals due to their hand-to-mouth activity and higher metabolic rate (3). They also have immune systems which are yet to develop completely (3). Their exploratory or probing behavior and ignorance of impending risks maximize their contact with harmful chemicals in the environment during developmental period (3). Recent decades have witnessed an unusual spurt in the incidence of genital malformations, infertility due to low semen quality, adverse pregnancy outcomes, neuro-behavioral disorders associated with thyroid disruption, endocrine-related cancers (breast, endometrial, ovarian, prostate, testicular, thyroid), premature thelarche, obesity and Type II diabetes mellitus (4). Congenital disorders such as cryptorchidism, hypospadias, early puberty and thyroid dysfunction have also been shown to have clear endocrine association (1-3).

Common examples of exposure to EDCs include Bisphenol A used in the manufacture of polycarbonate plastics and epoxy resins which have been found to be causative for obesity and polycystic ovarian syndrome (2,7). Phthalates used in nail polish, hair spray, deodorants and shampoos have been found to be associated with impaired genital development in male children (7). Lavender and tea tree oil on repeated use can stimulate estrogenic activity and cause male pubertal gynaecomastia (7). Flame retardants used in car seats and table pads may be inhaled by or absorbed through the skin of the baby and cause a greater risk of tumors (7). Early exposure to lead has been found to cause significant changes in hypothalamo-pituitary-adrenal axis while maternal smoking has been associated with obesity (7).

Apart from the above examples, some of these chemicals such as persistent organic pollutants (POPs), methylmercury which enter the bodies of younger children persist for a longer time due to their long half-lives and present their harmful effects later in life or cause multigenerational effects (2,3). The Stockholm Convention (2011) ratified by the international community recommended the elimination or phasing out of POPs (3). Some EDCs like dichloro-diphenyl-trichloroethane banned years ago in some countries, still persist in the environment and human bodies and manifest in older age groups (7).

Characteristics of Endocrine Disrupting Chemical Exposure

EDCs often produce their impacts with relatively low doses (3,7). Most EDCs do not have traditional dose-response curves (3,7,8). The timing of exposure decides the magnitude of impact (3,7,8). Effects such as learning difficulties, increased susceptibility and sensitivity to infections, testicular dysgenesis syndrome, infertility, fibroids, premature menopause, obesity, atherosclerosis, cardiovascular disease, Alzheimer's disease, Parkinson's disease, breast and prostate cancers manifest after a variable latent period depending on the time and the specific tissue exposed (3,7). Multi-chemical exposures are frequent and often have additive or synergistic potential (3,8).

Challenges

A large number of EDCs and their sources are yet to be identified. The effects of human exposure and their mechanisms of action have not been clearly understood for many EDCs. There are no clear guidelines for testing the effects of EDCs. The most challenging aspects of EDCs are their ubiquitous nature and exposure, their ability to cause a wide range of health effects with minimal doses, and the persistence of the resulting biological effects which are sometimes multigenerational (7).

Actions Required

Prevention of exposure is the single most effective measure to protect children against these toxic chemicals. But prevention of exposure may not be an immediate possibility due to the ubiquitous and often masked presence of EDCs in the environment. Exposure control could be effectively implemented as a short-term measure. Exposure control of lead has been found to have proven favorable consequences (4). Table I discusses the strategies and actions required to efficiently control EDCs.

All the above measures would be incomplete without sensitizing the health care workers and health professionals who encounter children in their day-to-day practice.

Pediatricians, general health practitioners and other health-care personnel are a significant resource-group with frequent contact with individual families. They have to be sensitized to enquire about the child's environment with specific queries for EDCs apart from regular arthropods and insects (3). History-taking at the onset of reproductive disorders should include careful assessment of occupational and environmental exposure of the individual and the close family (8). Pediatricians can play a role in promoting the development of model programs and

Table I. Overview of strategies and actions required to control endocrine disrupting chemicals

Strategies	Actions required
Strengthening knowledge on EDCs (4)	-Knowledge on EDCs should be imparted to all streams of students in schools and colleges. -The general population should be educated through mass media and local representatives. -Community level decisions and strict adherence are required for safe use of substances involving EDCs. -Production and consumption of organic food products should be encouraged.
Enabling research environment (4)	-To identify EDCs (4). -To identify methods to evaluate evidence (4). -To develop validated screening and testing systems (4). -To promote development of validated biomarkers (8). -To strengthen existing systems in accurate hazard identification and toxicity prediction (4). -Populations and communities with EDC exposure should be identified and exposure response studies should be conducted (8). Hotspots with unexpectedly high prevalence of suspected disorders should be watched for and identified early (8).
Reducing exposure and vulnerability (4)	-Community education, education of parents and teachers is an essential need. -Stringent regulatory measures for manufacturing and processing units to curb the use of toxic chemicals and promote the use of harmless, neutral substitutes. -Restrain indiscriminate discharge of effluents into the environment Implement strict measures to motivate manufacturers in proper labelling and declaration of constituent ingredients of products (4). -Consumers should be educated to peruse the relevant ingredient details (4). -Promote safe agricultural practices with the restriction of the use of pesticides and other chemicals.
Commitment from policy-makers	-EDCs with proven toxic effects have to be banned. -For EDCs where total ban is impossible, an initial ban of residential use can be promoted. -Substitution with non-toxic or less toxic substances should be promoted. -Develop guidelines for the disposal of industrial, agricultural and pharmaceutical waste and ensure their strict implementation (3). -Enabling intersectoral coordination for efficient implementation of programmes. -Poverty alleviation measures to enable improved housing, cooking fuel to help avoid environmental exposure. -Provide simple, specific messages and guidelines for general public to help them protect themselves.

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practices in the communities and schools of their patients (9). An integrated team approach involving pediatricians, clinical endocrinologists, environmental toxicologists and epidemiologists will strengthen study designs and help in the increased understanding of the associations (10).

While it is a substantial challenge to identify and regulate the use of these chemicals, immediate and effective measures against EDCs provide a tremendous opportunity to improve child health and contribute to a healthy human resource. It is the supreme responsibility of today's citizens, national and international governing bodies to recognize and act upon this imminent threat to child health and provide our children with a healthy future.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Geetha Mani, Design: Geetha Mani, Raja Danasekaran, Literature Search: Geetha Mani, Kalaivani Annadurai, Writing: Geetha Mani, Review and Approval of the Final Draft: Geetha Mani, Raja Danasekaran, Kalaivani Annadurai.

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References

1. World Health Organization. Possible developmental early effects of endocrine disrupters on child health. Geneva, World Health Organization. 2012. Accessed from www.who.int/phe/en Last accessed on November 1, 2016.
2. Newbold RR. Developmental exposure to endocrine-disrupting chemicals programs for reproductive tract alterations and obesity later in life. Am J Clin Nutr 2011;94(6 Suppl):1939S-42S.
3. World Health Organization. Children's Health and Environment. WHO Training package for the Health Sector. World Health Organization, Geneva. 2011. Available at www.who.int/ceh Accessed on November 2, 2016.
4. United Nations Environment Programme and World Health Organization. State of the Science of Endocrine Disrupting Chemicals 2012. Summary for Decision-Makers. Geneva, World Health Organization. 2013. Available at www.who.int/phe/en Accessed on November 1, 2016.
5. World Health Organization (WHO). Global assessment of the state-of-the-science of endocrine disruptors. Geneva, WHO, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html Accessed on April 15, 2014.
6. Amaral Mendes JJ. The endocrine disrupters: a major medical challenge. Food Chem Toxicol 2002;40:781-8.
7. National Institute of Environmental Health Sciences. Child development and environmental toxins. Available at http://www.niehs.nih.gov/health/assets/docs_a_e/child_development_and_environmental_toxins_508.pdf Accessed on November 2, 2016.
8. Diamanti-Kandarakis E, Bourguignon J, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293-342.
9. Pesticide exposure in children- Policy statement. American Academy of Paediatrics. Paediatrics 2012;130:1757-63.
10. Fleisch AF, Wright RO, Baccarelli AA. Environmental epigenetics: a role ain endocrine disease? J Mol Endocrinol 2012;49:R61-7.