EDC: Background and Introduction

EDC encompass a broad scope of chemicals, natural and otherwise. And while much of their certain effects are unknown, it has become clear that EDC have grabbed the attention of at least the scientific community. According to the Endocrine Society’s Scientific Statement on the matter, an endocrine disrupting chemical is “a compound, either natural or synthetic, which through environmental or inappropriate developmental exposures alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment.”

EDC can complicate the body’s various signaling processes in a variety of ways, including mimicking or interfering with the function of hormones. In addition, EDC can under or over signal processes, especially those carried out by hormones. These disruptions can have a significant impact on many different systems in the body, since endocrine signals are used in functions all over the body. Thus, EDC have been attributed to many health defects including many hormonally-related diseases: reproductive cancers, disrupting any hormonal signals to receptors, and abnormalities of the reproductive system. Another confounding aspect of EDC is their dissimilarity. Predicting which chemicals will act as EDC is difficult or impossible because there seem to be no distinguishable linking factors between these chemicals. As with all environmental science, there is continuing debate on the reality of EDC. There are numerous environmental and genetic conditions that can elicit the same biological change that can be attributed to an EDC.

The following is a list and explanation of the EDC that can commonly be found in drinking water.

- **Triclosan** – This chemical is present in soap, deodorant, toothpaste, shaving cream, and mouth wash. Triclosan can possibly combine with chlorine in tap water to form other chemicals. Furthermore, this chemical is linked with affecting metabolism through the thyroid gland.

- **Perchlorate** – This chemical can be found in rocket fuel, road flares, and fertilizer. According to a study performed in 2005 in the United States, this EDC contaminates the drinking water of approximately 40.8 million people. This EDC is linked with affecting the thyroid gland.
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- **Alkylphenol polyethoxylates** – These chemicals are present in industrial detergent, laboratory detergent, lubricant, and pesticide. Conventional sewage treatment will remove some of this chemical. These chemicals are linked to problems with estrogens and progesterones.⁶

- **Phthalates** – These chemicals are used very extensively. They are present in air fresheners, plastic toys, cosmetic and personal care products, vinyl, medical devices, inks and adhesives, food additives, and pesticides. Ironically, the EPA has had very little regulation of these, and in fact, the only one related to drinking water that is currently regulated – bis(2-ethylhexyl) phthalate – is not regulated as an EDC. The major phthalate is bisphenol A, and is heavily associated with the food industry: resin lining in all food and beverage cans, plastic baby bottles, Sippy cups, clear plastic water bottles, and kitchenware (measuring cups, storage containers). In fact, it was reported to be present in 30% of all samples in a national groundwater sampling. This chemical is related to EDC issues regarding androgen and progesterone receptors.⁵

- **Steroid hormones** – These chemicals, such as estriol, are present in the environment due to use on livestock. This EDC has possibly the least managed path to surface waters which then contaminate drinking water. Because it is used in hormone-enhancing products for feed animals, the waste produced by these animals frequently contaminates nearby groundwater sources. This chemical is associated with a wide range of hormonal receptors, including those affecting the production of estrogen, androgen, and progesterone.⁵

The Endocrine Process

Initially, EDC were thought to only be associated with nuclear hormone receptors and their functions. The most apparent affected processes include estrogen receptors, androgen receptors, progesterone receptors, thyroid receptor and retinoid receptors.

Estrogen receptors are cytoplasmic proteins that bind estrogens, which are most responsible for female characteristics, and migrate to the nucleus where they regulate DNA transcription. Androgen receptors are proteins, generally found in the cytoplasm that specifically bind androgens, which are most responsible for male characteristics, and mediate their cellular actions.

Progesterone receptors are specific proteins found in or on cells of progesterone target tissues that specifically combine with progesterone, which are related with the menstrual cycle, pregnancy and embryogenesis; the cytosol progesterone-receptor complex then associates with the nucleic acids to initiate protein synthesis.

Thyroid receptors are usually found in the nucleus, regulate DNA transcription, and are most readily associated with metabolism. These receptors are activated by hormones that lead to transcription, cell differentiation, and growth suppression.

Finally, retinoid receptors are proteins, dealing mostly with vision and bone growth, in the nucleus or cytoplasm that specifically bind retinoic acid or retinol and trigger changes in the behavior of cells.³ As stated previously, EDC have only, until recently, been associated with hormonal activity; now, it is apparent that EDC exposure may have a much wider impact on the body's endocrine system, including health problems, such as: non-reproductive cancers, immune effects, metabolic effects, diabetes, obesity, cardiovascular disease, and brain
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devlopment and behavior.\textsuperscript{2}

EDC can impact the body in these ways through a variety of approaches. They can:

“Mimic a natural hormone, fooling the body into over-responding to the stimulus (e.g., a growth hormone that results in increased muscle mass) or responding at inappropriate times (e.g., producing insulin when it is not needed)”\textsuperscript{4}

“Block the effects of a hormone from certain receptors (e.g. growth hormones required for normal development)”\textsuperscript{4}

“Directly stimulate or inhibit the endocrine system and cause overproduction or underproduction of hormones (e.g. an over or underactive thyroid).”\textsuperscript{4}

**Key Effect Issues**

There are three main effects of exposure to EDC that need further studying. These key effect issues are: age at exposure, long-term latent effects, and effects of low doses.

- **Age at Exposure** – The age at exposure to an EDC seems to largely influence the reaction to the chemical. It is difficult to accurately link cause and effect for EDC because of the idea of “latency of exposure,” meaning that there is a large gap of time between exposure to the EDC and its tangible effects on the body, if any. Scientists have termed this concept “the developmental basis of adult disease.” In other words, humans exposed to EDC at an early age may develop serious issues much later in life. This seems to be due to the sensitivity of the body to hormonal signals during pre-life, developmental, and infant stages of life.\textsuperscript{1}

- **Long-Term Latent Effects** – While latency of exposure may impact a single person by showing health problems much later in life, the long-term latent effects of EDC can have an effect on many people. Since EDC target factors which regulate gene expression, the modifications may be passed on. Thus, the exposure of one person to a particular EDC may have medical implications on future generations.\textsuperscript{1}

- **Effects of Low Doses** – Another oddity of EDC is there uncommon dose-effect distributions. Most adverse chemicals’ effects worsen with increasing dose, but this is not necessarily the case with these chemicals. Endocrine signals deal with incredibly small changes in hormone levels. Thus, chemicals which disrupt these biological signals need not be present in large amounts to have a lasting or serious impact. Furthermore, effects can be seen with one-time exposure.\textsuperscript{1}

**EDC In Drinking Water**

EDC can be a danger to human health through their presence in drinking water for two reasons. First, EDC can be found in a myriad of common, everyday products. Second, many wastewater treatment facilities do not treat for these chemicals, and if they do, the treatment is incidental and does not have the ability to remove a large enough percentage of the chemicals from the water stream. This, again, refers back to the concern that EDC
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can have serious adverse health impacts in low doses.

EDC Debates in Science and Medicine

In the scientific and medical communities, there is no question about the risk of EDC. It is certain that these chemicals could cause many health issues through the altering of hormonal conditions. The question and debate going on currently in the professional world, however, is how serious the risk of these chemicals is. Because the recognition of EDC is rather new, there has not yet been enough investigation or thorough testing to understand exactly how dangerous certain EDC are. Currently, most testing has been performed, “in vivo,” on rodents and primates. This testing demonstrates biological effects consistent with the pathophysiology suggested for human disorders. These results are also partially supported by human epidemiological studies, regarding such health issues as hypospadias and cryptorchidism, both common congenital anomalies. However, because of some inconclusiveness, this research has only been enough to recognize the authenticity of EDC; it cannot speak firmly enough to how much attention and care can or should be given to the situation.

Another major issue of EDC is the difficulty of identifying them and determining their sources. As was previously stated, EDC are varied and different. Another point to understand is that EDC come not only from contamination and pollution, but from natural sources as well. For example, many soy-based food products contain EDC. Furthermore, because there may be latent health effects from EDC exposure, it can be very difficult to link cause and effect. The harder it is to easily identify EDC, the more laborious and time-consuming the research process becomes. The lack of evidence or exact knowledge on the subject has delayed final decision-making regarding the need for regulation.

EPA Actions: Past and Present

The most prominent effort made by the United States Environmental Protection Agency (EPA) to handle EDC was the establishment of the Endocrine Disruptor Screening Program (EDSP). This program was set up by the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). In 1998, the EDSTAC created the screening program, but it has yet to be implemented. This delay is chiefly due to ensuring that all screening and testing processes are accurately validated.

Currently, the EPA is finalizing the first tier of its two-tier review process. “Tier 1” involves creating a large list of potential EDC, and screening these chemicals to determine if they are endocrine disruptors. Test order, for a list of 67 initial chemicals, were published from October 2009 to February 2010 to various private companies. As proposed, these tests must be completed within 24 months of when the test order was received. The tests include:

Amphibian Metamorphosis (Frog) - The Amphibian Metamorphosis assay involves the use of tadpoles to determine if chemicals affect the hypothalamic-pituitary-thyroid (HPT) axis during metamorphosis and consequently result in developmental effects.
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Androgen Receptor Binding (Rat Prostate) - The androgen receptor (AR) is involved in the development of male sexual characteristics. The AR Binding assay identifies chemicals that affect the endocrine system by binding to hormone receptors to either mimic the action of the natural hormone or block access of the hormone to the site and thus block hormone controlled activity.

Estrogen Receptor Transcriptional Activation (Human Cell Line (HeLa-9903)) – The estrogen receptor (ER) is involved in female maturation and reproductive function. The ER Transcriptional Activation is a cell-based assay that measures the ability of a chemical to bind to the ER and activate transcription resulting in the synthesis of the enzyme luciferase.

Fish Short-term Reproduction -The Fish Short-term Reproduction assay screens for disturbances in the hypothalamic-pituitary-gonadal (HPG) axis including (anti-)estrogenic, (anti-)androgenic, aromatase inhibition, and steroid modulating effects. The assay examines abnormalities associated with survival, reproductive behavior, secondary sex characteristics, histopathology, and fecundity (i.e., number of spawns, number of eggs/spawn, fertility, and development of offspring) of fish exposed to test chemicals.

Hershberger (Rat) - The Hershberger assay is designed to detect androgenic and anti androgenic effects. In this in vivo assay, the weight of several androgen-dependent tissues, including accessory sex glands, are measured in castrated or immature male rats.

Female Pubertal (Rat) - The Pubertal Female assay involves the use of rats to screen for estrogenic and thyroid activity in females during sexual maturation. This assay examines abnormalities associated with sex organs and puberty markers, as well as thyroid tissue.

Male Pubertal (Rat) - The Pubertal Male assay involves the use of rats to screen for androgenic, anti-androgenic, and thyroid activity in males during sexual maturation. This assay examines abnormalities associated with sex organs and puberty markers, as well as thyroid tissue.

Steroidogenesis (Human Cell Line – H295R) - The Steroidogenesis in vitro assay detects interference with the body's production of male and female steroid sex hormones. This assay is a cell-based assay using the H295R human adrenocortical carcinoma cell line which can detect inducers of enzymes responsible for steroid synthesis as well as chemicals that inhibit it.

Uterotrophic (Rat) - The Uterotrophic assay involves the use of female rats to screen for Estrogen Receptor Transcriptional Activation (Human Cell Line (HeLa-9903)) – The estrogen receptor (ER) is involved in female maturation and reproductive function. The ER Transcriptional Activation is a cell-based assay that measures the ability of a chemical to bind to the ER and activate transcription resulting in the synthesis of the enzyme luciferase.

Estrogen Receptor Binding -The estrogen receptor (ER) is involved in female maturation and reproductive function. The ER Binding assay measures the ability of a chemical to bind to the estrogen receptor.
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There is some concern that even now, the tests being used to identify EDC may not be as ready to be used as would be hoped. Never the less, those working on the procedures had deadlines to meet and so the screening began. One important note to emphasize is the difference between Tier 1 and Tier 2. Tier 1 screening only identifies possible EDC, but does not prove that said chemicals are certainly harmful.8

Tier 2, takes those chemicals identified as EDC and uses further testing to make judgments regarding the magnitude of adverse effects. Some Tier 2-like testing has begun on some of the initial 67 chemicals. It will be many years before we see the results of the testing. There will also need to be validation and further testing of Tier 2 procedures to ensure the accuracy of the information. The EDSP hopes to create a list of serious EDC that can then be used to educate and create regulation of the correct chemicals.8

There has been some discussion of expanding the initially screened chemicals. However many are concerned that screening more chemicals could be rash – especially if the testing method may encounter some difficulty. Several scientists see an expansion of screening to include more, non-pesticide chemicals as premature, unnecessary, and costly.8

Possible Future Regulation

- Because there will be more testing on EDC, any regulation of EDC will not occur for many years. The Toxic Substance Control Act ("TSCA") will be the most likely foundation for any regulation. TSCA currently regulates the introduction of new or already existing chemicals into the environment and the stream of commerce. There has been some push and encouragement for more regulation of EDC through TSCA.
- The Safe Drinking Water Act ("SDWA") has also been identified as another area in which the EPA has the authority to more rapidly regulate EDC. Under the SDWA, the EPA can test any substance that may be found in sources of drinking water that has a substantial potential of exposure and harm. Currently, EPA is preparing a list of at least 100 chemicals for testing under the SDWA.8
- The National Pollutant Discharge Elimination System, under the Clean Water Act, may also serve as a foundation for regulation of EDC. The Pretreatment Program regulates and establishes “responsibilities of Federal, State and local government, industry and the public to implement Pretreatment Standards to control pollutants from the industrial users which may pass through or interfere with publically owned treatment works (POTW) treatment processes or which may contaminate sewage sludge.”9
- The only significant political reaction to any public concern of EDC came in the form of H.R. 419010 and S. 282811, both of which were introduced on December 3, 2009. These bills both say essentially the same thing: “To amend the Public Health Service Act to authorize the National Institute of Environmental Health Sciences to conduct a research program on endocrine disruption, to prevent and reduce the production of, and exposure to, chemicals that can undermine the development of children before they are born and cause lifelong impairment to their health and function, and for other purposes.”10 Both bills are still under review by their respective committees.
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