# A Critical Analysis of the Association between Endocrine Disrupting Chemicals and Human Metabolic Disorders

Ali A. Rizvi*

*Emory University School of Medicine, Atlanta, Georgia, USA*

**Abstract:** Endocrine-disrupting chemicals (EDCs) are synthetic compounds predominantly of human design that are capable of causing interference in the hormonal functions of living organisms. They have the potential for causing adverse effects on the metabolic, cardiovascular, neurologic, immunologic, hematologic, and reproductive systems in the human body. Early exposure can impact growth and development and alter susceptibility to disease that may be pervasive and immutable. Reduction or augmentation of hormone action at the molecular, cellular, or systemic level can occur, leading to interference with signaling and feedback loops. EDCs can impact the production, secretion, transportation, action, or elimination of hormones. The endocrine system may be affected by EDCs from pesticides, plastic components, food additives, preservatives, soaps, detergents, pharmaceuticals, cosmetics, and even health supplements. These chemicals may gain entry into the human body through inhalation, ingestion, or absorption through the skin and mucous membranes. Metabolic disorders thought to be linked to EDC exposure include brain neurotransmitter dysfunction, appetite dysregulation, weight gain, obesity, glucose intolerance, metabolic syndrome, dyslipidemia, and cardiovascular diseases. Assessment and recommendations from the manufacturing industry, regulatory agencies, and the scientific community are ongoing in an effort to further understand and possibly mitigate the adverse consequences of EDC exposure. Further research is imperative to gain insight into the impact of EDCs on human health. A brief review of the metabolic and endocrine target systems thought to be affected by these chemicals as they have made their way into the everyday fabric of human society over the past century is given.

**Keywords:** Endocrine-disrupting chemicals, hormone, metabolism, diabetes, obesity.

## INTRODUCTION: WHAT ARE ENDOCRINE DISRUPTING CHEMICALS?

Endocrine-disrupting chemicals (EDCs) can be defined as exogenous chemicals, or mixture of chemicals, that interfere with any aspect of hormone action [1]. Endocrine disrupting activity can be attributed to a multitude of environmental chemicals that are scattered in our environment and have the potential to enter living organisms and interact with mammalian hormonal systems.

The evaluation of EDCs is fraught with controversy even though accumulating evidence points to an increasing role of these compounds on the environment and on human health [2]. Scientists, consumer groups, and government agencies have different approaches and agendas when it comes to examining this arena. On the one hand, one can examine the effects of compounds produced artificially for industrial and domestic consumption purely from a chemical perspective. Mechanistic aspects would thus be paramount. On the other hand, industry and the manufacturers of utility products view this from the aspect of harm prevention and safety. Biologic and mechanistic explanations are available mainly via animal models. Occasionally, occupational or accidental exposure to certain chemicals with hormone-altering properties, although unwanted, gives a peak into a window of pathologic processes that have a biochemical basis. What follows is an overview of these products with regard to human health with particular emphasis on the endocrine system. A description of the epidemiological associations between exposure to EDCs and human disease is presented.

## AN OVERVIEW OF THE ENDOCRINE-METABOLIC SYSTEM

The major endocrine glands (ductless internal organs that release hormones directly into the circulation) are devoted to regulating physiologic processes and are distributed throughout the body. The wide array of developmental, metabolic, and homeostatic functions regulated by hormones include growth, cell differentiation, glucose, fat, and protein metabolism, thermostasis, steroidogenesis, the stress response, sexual and reproductive function, puberty, cartilage and bone processes, and even brain and cognitive function. Most hormones act on specific receptors and act as signaling molecules for downstream intracellular cascades. Many functions performed by hormones are critical in health and disease. Indeed, endocrine gland failure results in underactive or deficiency states, while overproduction has the opposite effect of excessive amounts and disturbed homeostasis, result from subphysiologic and

*Address correspondence to this author at the Emory Johns Creek Hospital, 6335 Hospital Parkway, Johns Creel, GA 30097, USA; Tel: 404-778-2064; Fax: 404-251-1260; E-mail: arizvi4@emory.edu

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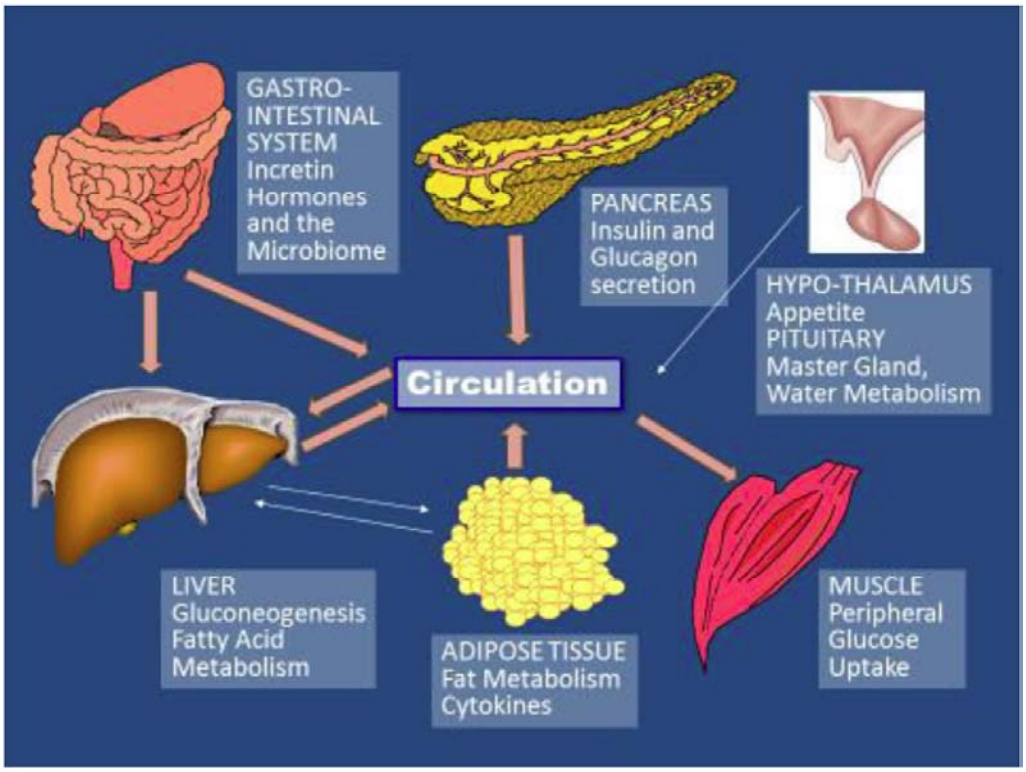


**Figure 1:** The Major Endocrine Glands that are involved in Regulating the Hormone-Metabolic Systems.

supraphysiologic states, respectively. Since target receptors are amenable to mimicry and manipulation, they are necessarily relevant to the action of EDCs. As an example, hormones have binding affinity to receptors, evoking a maximal response in the cells even at partial attachment. The complex intertwinement of hormonal action with regard to receptors, downstream actions, and negative feedback is depicted in Figure **1**.

Two fundamental mechanisms that prevail in endocrinology are the dose-response curve (with usually the hormone levels being within the physiological range to be effective), and the negative feedback loop [3]. The latter is a tightly-regulated control system that allows maximal functional optimization in healthy states (Figure **2**), but which is subject to derangement at the molecular or macro-organ level. It is also the aspect which can be disturbed in a subtle manner when exogenous compounds like EDCs gain entry into the tissues and exert a competitive or pathophysiological effect [4].

## HOW DO EDCs PROMOTE ENDOCRINE-RELATED DISEASE?

EDCs likely initiate pathogenesis by a variety of mechanisms, not all of which are entirely understood. EDCs cause perturbations of the delicate interaction between genes and the environment that lead to biochemical imbalance [5]. With respect to the action of hormones, they disrupt homeostasis and alter physiology [6]. EDCs enhance, dampen, or block the action of hormones by binding to the former's receptors and subsequently acting either as agonists or antagonists [7].

Some EDCs alter the expression of hormone receptors in different cell types and may also impact the effective concentration of circulating hormones [8]. Alternative phenotypes may potentially emerge if the timing and exposure is conducive, leading to increased susceptibility to disease. If such exposure occurs during ontogenesis, it can induce long-term changes in the development and function of organ systems, leading to unpredictable consequences [9]. Hormonal signals cause changes in mammalian target cells at the molecular level during certain critical periods which can modify gene expression or act epigenetically to affect structural and functional aspects of tissue function [10]. EDCs actions may reprogram essential signaling/differentiation pathways during this vulnerable time and lead to lifelong consequences [11]. Molecular changes preceding gene or protein expression in response to EDCs lead eventually to morphological variations and eventual disease manifestations over the course of the organism's lifetime.

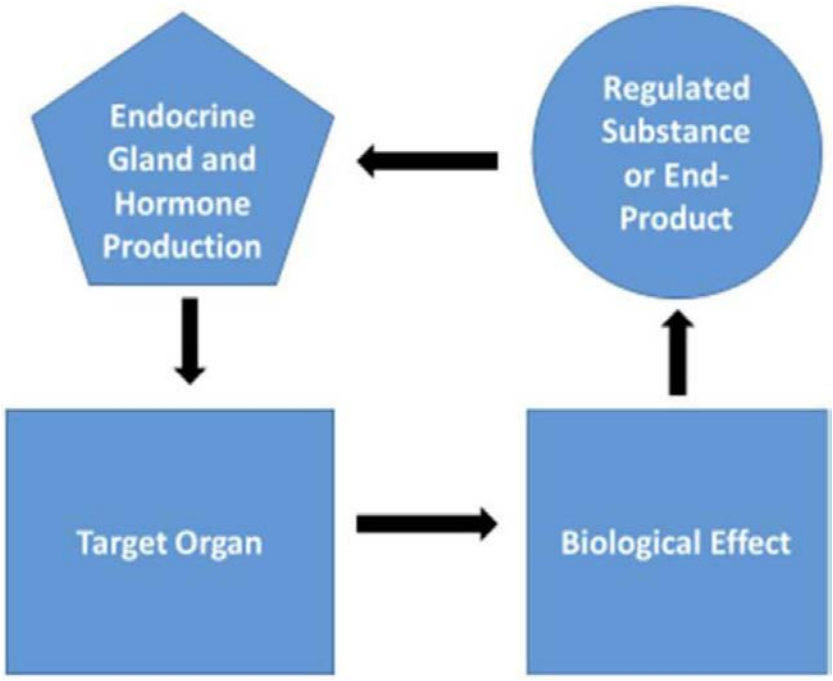


**Figure 2:** The Negative Feedback System in Hormonal Self-Regulation for maintaining Homeostasis.

There is a plethora of circumstantial as well as measurable evidence that developmental and adult exposure to EDCs such as BPA, phthalates, PCBs, pesticides, dioxins, and tributyltin (TBT) may increase disease susceptibility by causing endocrine disruption at the ligand-receptor-signal level [12].

A synopsis of some of the common EDC compounds is given in Table **1**.

The majority of the population is exposed to chronic, low-dose amounts of these chemical over a lifetime. Genetic and environmental variables combine to formulate the final impact that on the complex endocrinologic feedback loops in the human organism. Susceptibility to common noncommunicable diseases (NCDs) is increased from early EDC exposure, leading to permanent physiological changes through the gene-environment interplay [13]. Single nucleotide polymorphisms (SNPs) in the genome are related to incidence and severity of cardiovascular diseases, type 2 diabetes mellitus (T2DM), obesity, and abnormalities in metabolism, reproduction, and other endocrine systems. Each SNP has a small effect and these add up to cause disease manifestations [14]. Interestingly, these polymorphisms may also contribute to the organism's variability in the response to chemical exposure. Under the circumstances of chronic lifelong exposure, EDCs may elicit effects such as weight gain ("obesogens") and/or insulin resistance and hyperinsulinemia ("diabetogens"), thus predisposing individuals to endocrine abnormalities such as metabolic syndrome and T2DM [15].

## EPIGENETIC PROCESSES – EMERGING KNOWLEDGE

Recent research has tried to shed light on the epigenetic and subsequent transgenerational effects of EDCs on numerous organ systems [16, 17]. Epigenetic alterations are those that occur in gene expression but are not due to mutational changes in the DNA sequence. As a result of the high plasticity of the epigenetic code early in life, this period is susceptible to reprogramming through EDC-induced alterations that has repercussions all the way into adulthood [18]. They are heritable, with possible mechanisms including methylation of cytosine residues on DNA, post-translational modification of histones, and altered microRNA expression [19]. Both hormones and EDCs cause DNA methylation, histone modifications, and altered microRNA expression [20]. These epigenetic changes often cause phenotypic changes in organisms, which are dictated by the timing of exposure.

EDCs can permanently alter the germline in the epigenome during early development. These changes can be transmitted to subsequent generations. In adults, EDC-induced epigenetic changes occur in somatic cells; they are neither permanent nor transmittable to offspring [21]. EDC-induced epigenetic

**Table 1: Common Endocrine Disrupting Chemicals and their Uses**

| Major Endocrine Disruptor Groups | Use |
|---|---|
| Bisphenol A (Refs. [6,10,11,12])<br>*Polycyclic aromatic hydrocarbons* | Polycarbonate and epoxy resins used to make hard plastic items, such as baby bottles, re-useable water bottles, food containers, pitchers, tableware and other storage containers |
| Polychlorinated organic compounds (Refs. [5,6])<br>*Polychlorinated biphenyls (PCBs), Dioxins, Furans,*<br>*Polychlorinated naphthalene, Hexachlorobenzene, Octachlorostyrene* | Industrial and commercial applications: electrical, heat transfer and hydraulic equipment; plasticizers in paints, plastics and rubber products. Use was banned in 1979 |
| Brominated Flame Retardants (Refs. [2,4])<br>*Tetrabromobisphenol A, Hexabromocyclodecane, Polybrominated bisphenyl ethers* | Compounds with inhibitory effect on combustion chemistry and tend to reduce the flammability of products |
| Pesticides (Refs. [4,6,32])<br>*Organochlorines, Carbamates, Organophosphates, Tributyltin, Pyrethroids* | Used to reduce a variety of bacterial, fungal, and insect populations in plants and agricultural crops by adding to soil or spraying |
| Phthalates (Refs. [8,37,38,39])<br>*Di(2-ethylhexyl) phthalate, di-isononyl phthalate, Di-n-hexyl phthalate, Benzylbutyl phthalate, Dibutyl phthalate, Diethyl phthalate* | Solvents in vinyl flooring, adhesives, detergents, lubricating oils, automotive plastics, plastic clothes, personal-care products (soaps, shampoos, hair sprays, and nail polishes) |
| Organic solvents (Refs [6,30])<br>*Ethylene glycol ethers, Styrene, Toluene, Xylene, Trichloroethylene, Perchloroethylene* | Used in adhesives, anti-freeze, brake fluid, cleaning products, electronics cleaners, epoxies, floor polishes, inks, lacquers, metalworking fluids, paints, pastes and varnishes |
| Alkylphenolic compounds (Refs. [1,2,6])<br>*Alkylphenolic ethoxylates, Alkylphenols* | Industrial surfactants used as emulsifiers, detergents, pesticides, and in the processing of wool and metals |
| Metals (Refs. [1,4])<br>*Arsenic, Cadmium, Copper, Lead, Mercury* | A variety of applications |
| Others (Refs. [1,2])<br>*Benzophenones, Parabens, Siloxanes* | Sunscreens, inks<br>Preservative ingredients in cosmetic, personal hygiene products, food products and pharmaceuticals<br>Sealants, adhesives, coatings, plastics, food contact materials |

changes can also be dose- dependent and tissue specific [17]. In short, subtle genetic mutational variants of relatively low penetrance mutations at initial EDC contact lead to manifestations of a phenotype later in life.

Table **2** summarizes epigenetic processes and the associated chemicals that are known to influence them.

## DOSE-RESPONSE RELATIONSHIP

Since circulating hormones attach to high-affinity receptors, they need only act at very low concentrations to initiate important biological effects. With respect to EDCs, the mechanisms that are relevant to dose-response characteristics are dependent on a host of factors [22], foremost being the ease of delivery to the site of action. A monotonic response, where the effect is directly proportional to the EDC exposure, is much more the norm than the nonmonotonic responses [22]. Other aspects include receptor properties, such as number and isoforms, signal transduction requirements, and ligand characteristics. Nonlinear dose-responses are thus important as well.

For a multitude of reasons, it is difficult to define potency and thresholds when it comes to EDCs and

**Table 2: Animal and *In Vitro* Data of Epigenetic Associations (Ref. [16-21])**

| Type of Epigenetic Change | Causative Agent |
|---|---|
| DNA Methylation | Methoxychlor, di(2-ethylhexyl)phthalate (DEHP) |
| Histone Modifications | Paraquat, Dieldrin, Propoxur, Diethylstilbestrol (DES) |
| MicroRNA Expression | Bisphenol A (BPA), Dichlorodiphenyltrichloroethane (DDT) |

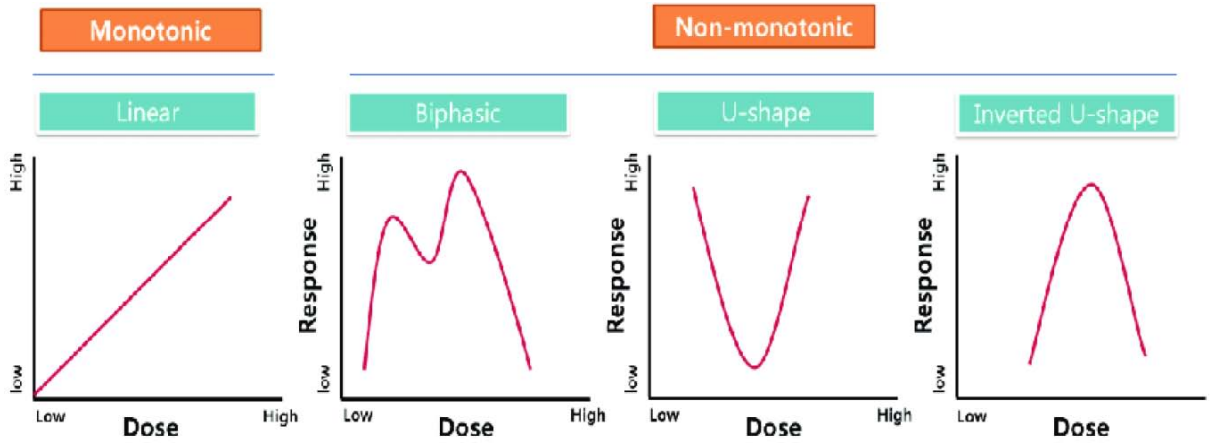


**Figure 3:** Dose-Response Curves Possibilities in EDC-Endocrine Receptor Action.

*From:* Low-Dose Exposure to Bisphenol A in Early Life. Yeon-pyo Hong and Yun-Jung Yang, authors. In book: Bisphenol A Exposure and Health Risks. Published by Intech. June 2017. DOI: 10.5772/intechopen.68428 (Reproduced without alterations under the Creative Commons License).

their actions [5]. Some endpoints of hormonal action are more sensitive to the hormone itself, while others are more likely to be affected by endocrine disruptors. Strong agonism means that very low concentrations of EDCs could augment endogenous hormone action to produce an exaggerated effect that is much greater than from its own binding. In outright antagonism, the hormone effect could be blocked completely or altered towards a different pathway.

The permutations of action and physiological effects in a dose-response curve relationship are depicted in Figure **3**.

## SOURCES AND TESTING FOR CHEMICAL ENDOCRINE DISRUPTION

Air, food, and water are all pervaded by EDCs, causing a wide number of endocrine disruption activities. Regular or recurrent exposure, for example due to environmental or occupational sources, may lead to higher amounts and from multiple entry points (lungs, skin, eyes, hair and nail appendages) [23]. Both humans and wildlife may suffer from pollution and accidental release from products, aerosolized as food residues after agricultural use, or find their way into milk from body stores [24]. Dermal penetrance is afforded by absorption of soaps, lotions, cosmetics, and sunscreens [25].

Potential sources of exposure of pertaining to specific materials that can go on to disrupt endocrine signaling are given in Table **3**.

The National Toxicology Program (NTP) and the European Union's 2007 REACH (Registration, Evaluation, Authorisation and Restriction of Chemical Substances) [26] have developed guidelines for using assays in the testing and regulation of potentially harmful chemical agents. The latter reached an agreement with industry regarding the improvement of specific environmental release categories (SPERCs) as an instrument for lower-tier environmental emissions assessment [27]. Typically, a dose range of the highest tolerable concentrations is used to look at endocrine-disrupting activity and toxic effects [28]. The United States Environmental Protection agency's Endocrine Disruptor Screening Program (EDSP) has developed a set of animal and cell-based assays to test EDCs [29] while The US EPA Toxicity Forecaster (ToxCast) and the Toxicity Testing in the 21st Century (Tox21) [30, 31] are two federally funded efforts that are studying chemicals for potential human health effects on a priority basis by unraveling signaling pathways and using cell-based assays.

Rodent models have been used to look at preliminary data concerning the long-term health effects of individual compounds. Testing schemes may incorporate assays to determine the potential of chemicals on hormones that act through signals on nuclear receptors. Such hormones encompass predominantly the thyroid, estrogen, and androgen. Other avenues include mitochondrial toxicity, the response to stress, cellular proliferation and growth regulators, drug metabolism, and peroxisome proliferator-activated receptor [PPAR]) [32].

Accidental exposures, although unfortunate and to be avoided, do afford an opportunity to analyze the untoward actions of EDCs, usually at higher levels than

**Table 3: Conduits of Human Exposure to EDCs (Refs. [23-31])***

| SOURCE | ROUTE OF EXPOSURE | EDCS PRESENT |
|---|---|---|
| Industrial Waste, Pesticides | Oral consumption of contaminated food or water | PCBs, dioxins, perfluorinated compounds, DDT |
| Pesticide residues in food or beverages; leaching of chemicals from food containers | Oral consumption of contaminated food or water | BPA, phthalates, chlorpyrifos, DDT |
| Flame retardants used to treat furniture | Skin contact and/or inhalation | BFRs |
| Pesticides use in agriculture, homes, or for pest control | Skin contact and/or inhalation | DDT, chlorpyrifos, vinclozolin, pyrethroids |
| Cosmetics, personal care products, anti-bacterials, sunscreens, medications | Dermal application | Phthalates, triclosan, Parabens, insect repellants |
| Maternal body burden due to prior/current exposures | Placental transfer | Numerous |
| Plastic intravenous tubing | Intravenous | Phthalates |

*Modified from: Introduction to EDCs: A guide for public interest organizations and policy-makers. David Crews, author. Available at https://www.researchgate.net/publication/269104905_Introduction_to_EDCs_A_guide_for_public_interest_organizations_and_policy-makers/link/5480c92e0cf20f081e72690e/download, accessed May 15, 2020.

usual environmental exposure. Mishaps have demonstrated a relationship between released chemicals and numerous documented health effects, including endocrine signaling endpoints. Significantly increased cancer rates, infertility, and metabolic issues in women [33] reduction in sperm quality in men [34] have been found. Examples of large-scale or sustained noxious exposures include the well-known Agent Orange exposure to US servicemen in South Vietnam, and a pesticide plant explosion in Italy in 1976 [35]. In the United States, decades of river contamination with PFOA in Kentucky and Ohio, and of residential drinking water sources with volatile organic chemicals in North Carolina have been documented [36].

## PROMINENT HORMONE-ALTERING CHEMICALS THAT IMPACT ENDOMETABOLIC PATHWAYS

### Phthalates

Phthalates and their esters are additive compounds that were first introduced as additives in the production of plastic almost a century ago, leading to the widespread use of polyvinyl chloride plastic thereafter. They are the dialkyl or alkyl aryl esters of phthalic acid with molecular formula $C_8H_4O_4^{-2}$ and molecular weight of 164.11 g/mol. They are used as liquid plasticizers in a wide range of products including plastics, coatings, cosmetics, personal care products, medical tubing, vinyl flooring materials, and toys. The reason that they are released into the environment is that they are not chemically bound to these products. Contamination in ice cream, frozen food, and cake mixes has occurred [37]. A major phthalate, di(2-ethylhexyl)phthalate (DEHP), may lead to an estimated daily exposure of 3–30 μg/kg/day [38]. Phthalates are detectable in human urine, serum, and milk [39]. Although they have relatively low accumulation in body fat tissue, they are easily detected in the majority of the population because of their widespread use.

### Bisphenol A

Bisphenol A (BPA) was first manufactured towards the end of the nineteenth century and is the chemical that is produced in the most quantities. It is an organic synthetic compound with the chemical formula $(CH_3)_2C(C_6H_4OH)_2$ and belongs to the group of diphenylmethane derivatives and bisphenols, with two hydroxyphenyl groups. It is a colorless solid that is insoluble in water but soluble in organic solvents. BPA can find its way into the human body though various sources, especially under high heat, physical handling, or repeated use, and most people get exposed to it on a continuous basis (6) [40]. It is utilized in manufacturing, food packaging, canned foods and beverages, and children's toys. BPA was discovered to have estrogenic properties; it is rapidly metabolized to inactive forms and has a half-life of about 5 hours in adults (12, 13) [41]. The majority of the population has a measurable amount of urinary BPA. Its prevalence in our daily environment has made it difficult to eliminate contamination even under controlled conditions (10, 11) [42]. Measurements of bioactive or free BPA in human serum is controversial at present. Internal exposure that is clinically relevant is still an unresolved but important aspect of monitoring. Individual variability in metabolism and susceptibility play a big role (17)

[43]. The US Environmental Protection Agency (EPA) has acted to raise awareness and set safe exposure standards for BPA under the Toxic Substances Control Act (TSCA) [44].

Animal studies have validate the epigenetic properties of BPA. Prenatal exposure to BPA hampered methylation in mice [45] and changed the DNA methylation of key genes that are associated with rat prostate cancer [46]. Reduced genomic methylation occurred in genes involved in immune function, protein transport, and metabolic activity in bisulfite-converted saliva DNA [47]; whether these result in abnormal phenotypes in subsequent generations is open to question.

### Atrazine

For the past 60 years, atrazine has been the major herbicide used worldwide since it is cheap, long-acting, and had a wide range of activity against weeds [48]. Its chemical formula is $C_8H_{14}ClN_5$, molar weight is 215.68 g/mol, and chemical name is 2-chloro-4-ethylamino-6-isopropylamino-s-triazine. It is an herbicide that is commonly used to control broadleaf and grass weed growth on crops such as commercial corn, sorghum, and sugar cane, as well as tree farms, parks, and golf courses. The potential of the chlorotriazines to affect aquatic organisms and their carcinogenic risk stems from groundwater contamination, since it is the most commonly detected pesticide in drinking water in the United States [49].

### Vinclozolin

Vinclozolin is a fungicide with antiandrogenic properties. The molecular formula is $C_{12}H_9Cl_2NO_3$ and the molecular Weight is 286.11 g/mol. Prenatal exposure to vinclozolin is known to cause transgenerational epigenetic changes in physiological and behavioral phenotypes in rodents [50]. Prenatal exposure to vinclozolin caused germ cell death and the appearance of diseased phenotypes in the prostate in males [51], while in females it leads to more ovarian cysts and a reduced number of oocytes and primary follicles [52]. It is to be kept in mind that these experiments used high-dose exposure to vinclozolin, the proposed mechanism being altered methylation of DNA [53].

## OBESITY, TYPE 2 DIABETES, AND CARDIO-METABOLIC DISEASE: LINKAGE TO EDCs

The past decade has seen an explosion of research implicating EDC exposure in the etiology of obesity and type 2 diabetes (T2DM). The hand-in-hand increase of pollutants and the rise in the incidence of metabolic issues paved the way for surmising that man-made, toxic chemicals promoted weight gain and contributed to the obesity epidemic [54]. It was hypothesized that exposure to environmental agents during early development (fetal growth and childhood) may play a role in predisposing to downstream weight gain later in life [55].

The nefarious actions of these so-called "obesogens" [56] were supported by evidence from epidemiological studies, animal data, and laboratory evidence at the cellular and molecular level. Some of these agents may be responsible for altered glucose metabolism as their predominant effect [57], having been labeled by some as "diabetogens." This term may be applied to any toxic chemical that kills β -cells or disrupts their function. For example, environmental chemicals such as dioxins, DDT, and BPA have been known to alter β-cell function for many decades [58].

Figure **4** lists some of the more prominent metabolically active EDCs and their pathways of action.

It is noteworthy that the connection between EDC exposure and alterations in glucose homeostasis may work through a variety of mechanisms, including aggravation of insulin resistance and perturbations at the hypothalamic and adipose tissue level. Animal studies as well as epidemiological analyses have lent credence to these possible pathways [59]. Because of interlinked pathologic cascades, there may be overlap between the role of these disruptors as risk factors for obesity, diabetes, and cardiovascular disease. Papalou and coauthors [60] have elegantly described the deleterious effects of EDCs on multiple components of human metabolism through cellular pathways that ultimately manifest as obesity, metabolic syndrome, T2DM, and nonalcoholic fatty liver disease (NAFLD) (Figure **5**).

*Obesity-promoting actions* of environmental chemicals may exert themselves during developmental life stages that are particularly prone and impressionable [53, 55, 61]. According to the "metabolic disruptor" hypothesis, environmental chemicals can act during development and other sensitive time periods across the lifespan to control adipose tissue development and/or by altering food intake and metabolism via specific effects on the brain, pancreas, adipose tissue, liver, gastrointestinal tract, and muscle individually or in combination [62].

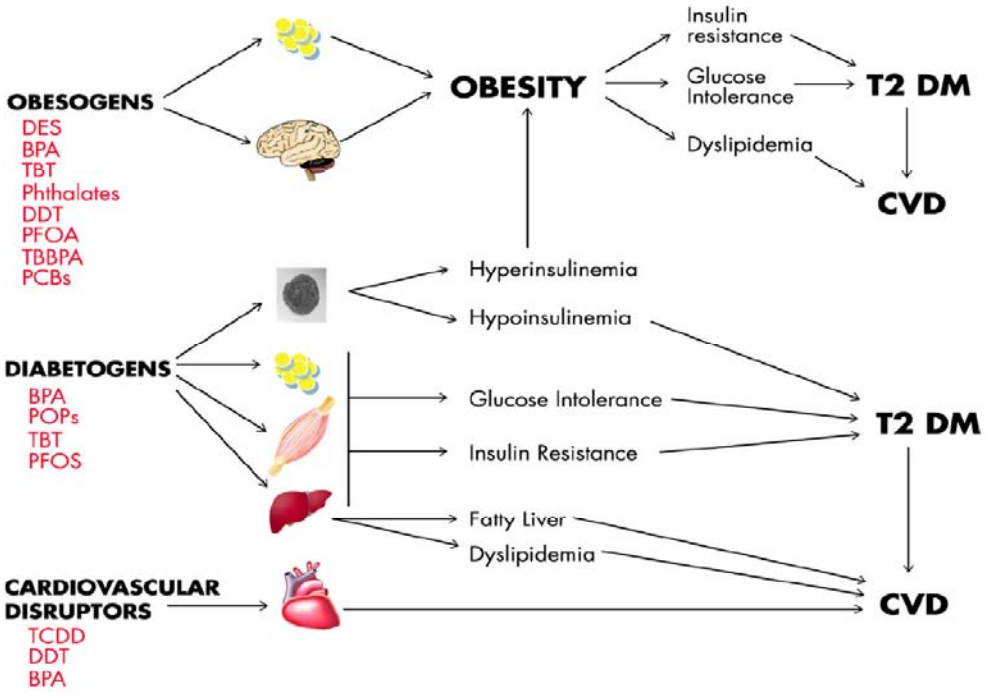


**Figure 4 – EDCs Acting as Obesogens, Diabetogens, and Cardiovascular Disruptors.** Copyright © 2015 by the Endocrine Society. From: *Endocr Rev*, Volume 36, Issue 6, 1 December 2015, Pages E1–E150, https://doi.org/10.1210/er.2015-1010.

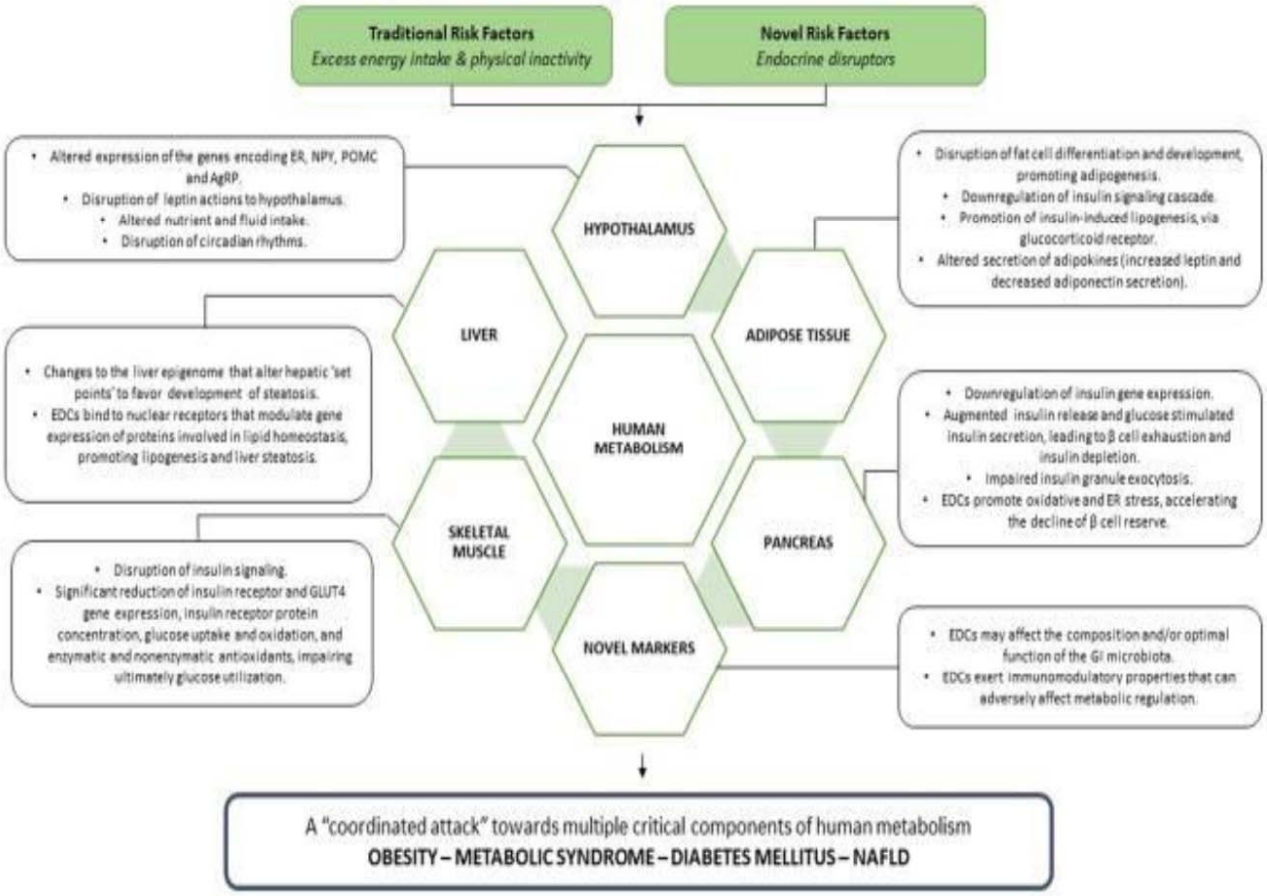


**Figure 5:** A Diagrammatic Representation of EDCs as Risk Factors for Human Dysmetabolic States. *From:* Front Endocrinol (Lausanne). 2019; 10: 112. Published online 2019 Mar 1. doi: 10.3389/fendo.2019.00112. Copyright © 2019 Papalou, Kandaraki, Papadakis and Diamanti-Kandarakis *(open-access).*

The close association of *NAFLD* with metabolic syndrome and T2DM has been recognized, even though its pathogenesis is incompletely understood [63]. EDCs could possibly promote NAFLD by acting as obesogens, or by direct actions on lipid metabolism and fat storage in the liver.

## ORGAN-SPECIFIC ACTIONS OF EDCs

### Pancreas

EDCs are known to negatively impact multiple aspects of insulin physiology in the pancreas, including β cell function, insulin resistance and glucose disposal. Dioxin exposure was shown to decrease glucose uptake in the pancreas, impair insulin secretion [64] and contributed to increased prevalence of glucose intolerance and hyperglycemia by causing pancreatic failure [65]. Apoptosis of islet cells may occur via multiple pathways. Beta cell function may potentially be reduced by BPA exposure. In rodent models, BPA may lead to glucose intolerance and altered insulin sensitivity as well as increased body weight [66]. As mentioned before, BPA has estrogenic properties and probably exerts part of its detrimental effects through hormone-dependent mechanisms [67]. An atmosphere of increased oxidative stress and inflammatory markers is enhanced by EDCs such as BPA, arsenic and DEHP, leading to compromised β cell function [68]. Immune-mediated disorders like type 1 diabetes may also be linked to EDCs and their immune-modifying properties [69].

### Liver

The deleterious effects of EDCs at the circulatory-hepatic interface promote the generation and deposition of fat in the liver parenchyma, ultimately contributing to the genesis of non-alcoholic fatty liver disease (NAFLD) [63]. The target of peripheral insulin resistance is perhaps most prominent in the liver, just as it is in striped skeletal muscle tissue. The liver is being increasingly recognized as a dynamic organ that secretes a wide range of metabolites, complex proteins, and noncoding messenger RNAs. A number of these factors have important roles in the interplay of metabolic processes between the liver and the peripheral tissues [70]. The efflux of lipolytic products such as lipoproteins and triglyceride-rich lipid fractions from the liver is an “overflow” state from an overfed organ that has tried to accommodate, but nevertheless overpowered by, an expanded adipose tissue mass. Reprogramming of the epigenome through the EDCs binding to specific nuclear hormone receptors in hepatocytes leads to recruiting co-regulator proteins and modulating gene expression involved in lipid homeostasis [71]. The final outcome is that EDCs can increase hepatic lipid accumulation and NAFLD in laboratory animals [72].

### Voluntary Skeletal Muscle

The muscular system is where the majority of insulin-mediated glucose disposal takes place and the insulin receptors and glucose transporter proteins are most active. Rodents exposed to BPA displayed disrupted insulin signaling through defective phosphorylation of insulin receptors [73]. In addition to data discussed above that demonstrated EDCs-induced derangements in insulin production and islet cell function, a large body of evidence suggests that mitochondrial function is also compromised [74]. Human exposure to BPA, TCDD, and phthalates has been causally correlated with insulin resistance in muscle tissues [68]. Insulin receptors, their substrates, and phosphatidylinositol-3-kinase form a chain of continuity in the signaling cascade and glucose transporter sequence that is impeded by EDCs [75]. As a consequence, fat deposition in skeletal muscle is an abnormal, multifactorial end-point state of resistance to insulin action.

### Adipocyte Function

The adipose tissue has come under intense research scrutiny in the past two decades as being an active organ that is the origin of complex, metabolically active hormones and cytokines. Interleukins and adiponectin are only a few of the adipocytokines that are mediators in the communication of adipocytes with the rest of the body. There is constant cross-talk between adipose deposits and the liver, muscle, gut, and brain. The end-result of these disruptive actions is increased inflammation, insulin resistance, hypertension, and dyslipidemia. The close relationship between adiposity and weight makes adipose tissues the principal target tissue of obesogenic chemicals. Modulation of adipocyte physiology, adipocyte genesis, and insulin action by EDC interference can induce and sustain chronic inflammation in metabolic disease [76]. EDCs such as DDT, BPA, phthalates, and PCBs can promote adipogenesis by disrupting fat cell differentiation and development [77], as well as disrupting the PPARγ pathway [78]. BPA promotes indirect effects on adipocyte physiology mediated by the glucocorticoid receptor by increasing mRNA

expression and enzymatic activity of 11β-HSD1 [79] and mimics corticosterone attachment to the same receptor [80]. EDCs can attenuate insulin signal transduction via especially down-regulating insulin receptor substrate-1 (IRS-1) levels [81]. In data gathered from animal models, endocrine disruptors have been demonstrated to modulate the actions of adipokines, insulin, and glucose, and impact body weight in male mice [82]. In human adipocytes cells, they have been demonstrated to inhibit *in vitro* adiponectin secretion [83] and upregulate proinflammatory pathways [84]. It is therefore, natural to assume that any exogenous substance that is even faintly lipophilic in nature will have the capacity to impact fatty tissue functions, potentially in a negative manner.

### Hypothalamic-Pituitary Function

Central appetite and feeding behavior may be impacted early in development or even *in utero* if exposure to EDC happens to occur [85]. Interference with the hypothalamic nuclei responsible for regulating food intake is probably the basis through interaction of the chemicals with nuclear receptors. BPA increases the vulnerability to environmentally-induced obesity (through precipitating compulsive eating), interfere with the hormone leptin, and aggravate metabolic dysfunction [86]. The estrogenic properties of BPA have been referred to as contributing to the disruption of hypothalamic feeding circuitry [87], and neonatal exposure of female rats to BPA led to downregulation of hypothalamic protein levels. Transgenerationally, adulthood can bring about DNA methylation of imprinted genes in the brain and epigenetic changes in their expression [88]. Thyroid regulation via the hypothalamus can impact energy homeostasis [89]. Thus, the role of EDCs in the central regulation of energy expenditure, nutritional intake, and the weight management is being unraveled and clearly needs further study.

### The Immune System

Evidence is accumulating that there is an intimate relationship between immune system and many aspects of metabolic disease [90]; disorders that lower the immune defense mechanisms are accompanied by metabolic dysregulation. The bulk of data is derived from immunomodulatory properties of EDCs in experimental animal models. Perinatal BPA exposure alter inflammatory and immune responses in rodents and can affect their propensity to disease in adulthood [91]. Adult rats exposed to BPA displayed increased proinflammatory cytokine levels in pancreatic tissue [92]. Both BPA and phthalates are inherently estrogenic and may impact cytokine levels. Similarly, the gut interface and its microbiome, which has come into the forefront of recent research, provides both a defense from, as well as a target of, EDCs [93]. Another major player in EDC-induced toxicity to the immune mechanisms is the intestinal bacterial microflora. “Beneficial” gut microbes use their protective shield to inactivate noxious EDCs by virtue of their enzymatic properties and minimize harm to the organism. On the other hand, potent EDCs may disrupt the composition and thus the barrier function of gastrointestinal microbiota and induce adverse metabolic effects [94].

## CONCLUDING POINTS

Human health has traditionally been impacted by the ravages of microbial disease, famine, pestilence, and warfare. Among other looming issues, technological progress since the Industrial Revolution has had two main unintended yet ominous consequences; environmental damage and the emergence of lethal weaponry. However, man-made disasters that are more akin to a “slow-moving catastrophe” encompass the widespread use and acceptance of chemicals used in industry, agriculture, and everyday life. Although only a little more than a century in common usage, it is becoming clear that compounds linked to consumptive ease, enhanced productivity, and consumer comfort may potentially be disruptive to normal endocrine and metabolic functioning. These dilemmas are ubiquitously global in nature and mounting evidence of their dangers cannot be ignored anymore. Issues like congenital defects, neoplasia, obesity, and noncommunicable metabolic conditions are fast becoming intimately linked to exposure to the more than a thousand known endocrine disruptors introduced in society. Research in this arena is now moving from the observational, laboratory, and epidemiological arenas to the establishment of causal relationships between exposure and metabolic disease. Further investigation and evidence-based regulation of industrial and domestic applications of EDCs seems to be the logical path and sensible strategy to mitigate adverse effects and ensure a healthier future for all life forms on our planet.

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