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Evaluating the Impact of Trans- and Multi-generational Exposure to Endocrine Disrupting Chemicals on Liver Development and Cancer Incidence

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ABSTRACT

Cases of liver diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD), Nonalcoholic steatohepatitis (NASH), fibrosis and liver cancers have increased by over 50% between the last three to four decades. In the United States, over one hundred million people are diagnosed with some form of liver disease. Endocrine disrupting chemicals (EDCs), substances that interfere with the endocrine system, are now ubiquitous in society, with detectable levels found in a wide range of industrial and consumer goods. Recently, there have been increasing amounts of evidence supporting trans and multi-generational effects of EDC exposure on human health, causing directly and indirectly exposed offspring to develop liver malformations, progressive disease and even cancer. This paper aims to summarize the relationship between EDC exposure and the incidence of liver diseases through multiple generations through inherited genetic and epigenetic alterations. Furthermore, possible treatments, methods of mitigation, and potential public policies concerning the use of EDCs in industrial manufacturing and their relation to human health will be discussed.

INTRODUCTION

EDCs interfere with human endocrine function and are associated with increased incidence of congenital malformations, cancer, and organ damage. In the United States, EDCs were first tied to porcine infertility linked to moldy grain consumption. This was not isolated to the US, as several international farmers observed similar incidents. It was later discovered that the grain contained mycoestrogens, fungal compounds that mimic estrogen in the body[1]. Thus, EDCs produce profound effects not only on human health, which will be emphasized throughout this review, but also on the health of other mammalian species.

One of the first examples of adverse EDC exposure on human development occurred in 1940, when pregnant mothers taking diethylstilbesterol (DES), a synthetic estrogen, gave birth to daughters who would develop a rare form of vaginal cancer in adulthood[2]. EDC exposure has also been linked to female

reproductive issues1. In the Jinzu river basin in Japan, higher environmental levels of cadmium were associated with premature births and in a separate study, a decline in chorionic gonadotropin secretion in adults[3,4]. EDCs are commonly used in industrial manufacturing[5]. For example, phthalates—diesters of 1,2-benzenedicarboxylic acid—are used in cosmetic products such as perfumes and lotions[6]. Another example of EDCs is bisphenols; a group of industrial chemicals used in the process of manufacturing plastics. For example, Bisphenol A (BPA) has been used since the mid-1900s for the production of plastics, epoxy resin, thermal paper receipts, and food packing[7]. Bisphenol F (BPF) and Bisphenol S (BPS) are BPA substitutes, and their usage has become more prevalent[7]. Moreover, there has been emerging evidence on the role of Bisphenols in the pathogenesis of other degenerative diseases, such as NAFLD. Recent studies have shown a positive correlation between urinary BPA levels and NAFLD severity. Additionally, EDC exposure during prenatal periods is correlated with higher levels of liver fat accumulation in the liver, liver injury, hepatocellular apoptosis, and several other liver diseases. Here, the role of EDCs on liver development and degeneration will be further discussed in detail.

METHODS

The literature used for this review paper has mainly been obtained through PubMed, a national database created by the National Center for Biotechnology Information (NCBI) in the U.S. National Library of Medicine (NLM). Original papers, literature reviews, and meta-analyses were reviewed in this paper and were found by using key words and phrases to search for information that I needed to structure this paper. Most references used were published in the last ten to fifteen years to ensure that the information reviewed is recent and not outdated. Some sources are older but have been checked to ensure that the information provided is still relevant.

While most of the references were retrieved by typing in key words in the search bar in PubMed, others were found as references in other papers. Since research and review papers are extremely specific to a certain goal or idea investigated by the authors, crucial pieces of information that were needed were not always found. To overcome this, keyword searches were used to find other papers that potentially had the information needed, and those papers were reviewed to determine if they were relevant.

ENDOCRINE DISRUPTING CHEMICALS: CHEMICAL MAKEUP AND BIOLOGICAL MECHANISMS

Chemical Structure and Inheritance of EDCs

Bisphenols are made up of a central bridging group with varying groups of linked phenol rings[8]. Bisphenol A has two methyl groups attached to a central carbon atom; Bisphenol F has two hydrogen atoms attached to a methylene bridge; Bisphenol S has a sulfonyl group as its central bridge. BPA has structural similarities to 17-β-estradiol [E2], and as a result can mimic some of its functions[9]. (**Fig. 1**)

Phthalic acid esters (PAEs) or phthalates—dialkyl or alkyl aryl esters of 1,2-benzenedicarboxylic acid—are a type of lipophilic chemical used as plasticizers and additives. Their structure usually consists of a rigid planar aromatic ring and two malleable nonlinear fatty side chains[10]. Phthalates can mimic structural features of testosterone and interact with human androgen receptors[11]. Per-/polyfluorinated substances (PFAS) are a series of organic compounds that have at least one perfluorinated carbon atom[12]. PFAS bind to transthyretin (TTR), a transport protein in the blood[13]. Thyroxine, a natural hormone, usually binds to TTR, but since PFAS are structurally like thyroxine, as they both have negatively charged tails with carboxyl groups, they will not be able to bind anything. (**Fig. 2**)

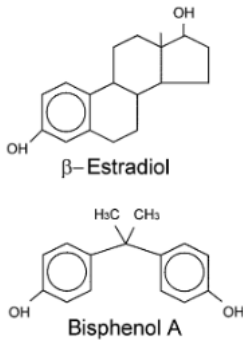

Figure 1. Chemical Structures of β-Estradiol and Bisphenol A. Figures adapted from[14].

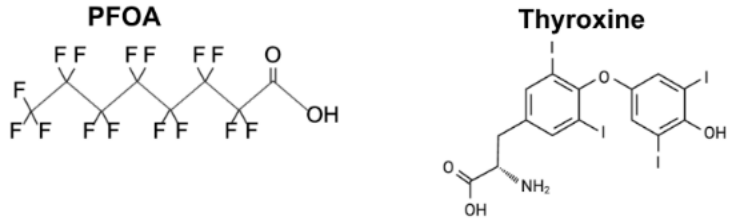

Figure 2. Comparing Chemical structures of Perfluorooctanoic Acid and Thyroxine. Image created using BioRender.

EDCs consist of natural and synthetic chemicals that disrupt hormone biosynthesis, action or metabolism, leading to altered physiological homeostasis and reproduction in humans. BPA, for example, is an estrogen mimic, meaning it can influence the activity of the estrogen receptors α and β (ERα/β), causing alterations in downstream gene transcription. Two methods of transcriptional gene regulation by ERs include the classical mechanism and the non-classical or "tethered" mechanism. In the classical mechanism of gene regulation, ERs bind to estrogen responsive elements located in the promoter area of target genes. The tethered mechanism involves gene expression by association with other transcription factors that bind to DNA[15]. Most EDCs from natural or synthetic sources have similar structures to endogenous steroid hormones (hormones the body builds from cholesterols) because of their phenolic structure, giving them a tendency to bind to hormone receptors both as agonists and antagonists[16].

When estrogen molecules bind to their receptors, they translocate into the nucleus and bind to short sequences known as estrogen response elements (EREs). These transcriptional co activators, which are proteins that bridge transcription factors and RNA polymerases, induce gene expression. When EDCs mimic estrogen, they can activate or repress estrogen-activated genes, resulting in dysregulation of genes involved in cell proliferation, metabolism, hormone synthesis, and reproductive health.

Multi- and Transgenerational Inheritance of EDCs

One of the largest concerns of EDCs is their ability to cause direct and indirect genetic changes that can persist through generations. Throughout developmental stages, EDC exposure has been linked to permanent heritable epigenetic changes to subsequent generations. When pregnant females (F0 generation) are exposed to EDCs, the fetus (F1) and fetal germ cells (F2) are directly exposed through multigenerational inheritance, while changes that persist into the F3 generation are considered transgenerationally inherited. Paternal exposure to the F0 generation results in direct exposure to the F1 generation (sperm cells) through multigenerational inheritance while the F2 generation is exposed via transgenerational inheritance (Fig. 3). In both human and animal studies, pregnant mothers exposed to Diethylstilbestrol (DES) gave birth to offspring presenting with increased weight and adipocyte hyperplasia[17,18]. Thus, EDCs may alter the function of adipose tissues through the alteration of (in)direct genetic or epigenetic reprogramming, respectively.

To determine the multi- and transgenerational effects of EDCs on juvenile behaviors in vivo, mice were exposed to BPA in the womb to levels relevant to human exposure. Mice in the F1, F3 and F4 generations demonstrated increasing levels of social investigation, possibly attributed to declines in social recognition memory associated with neurodevelopmental defects. Thus, BPA's neurological effects ensued through multiple generations possibly due to inherited epigenetic alterations[19]. In another study, pregnant female rats were exposed to either "plastics" or a "lower dose plastics" mixture (groups of three types of plastic chemicals with different amounts) during gonadal sex determination, which is a critical window of pregnancy when undifferentiated gonads develop into testes or ovaries[20]. In response to exposure, there was an increase in reproductive and organ-specific diseases in F1 and F3 offspring. F3 females demonstrated increased loss of primordial follicles with lower ovarian follicular reserve associated with infertility, shorter cycles and potential early menopause. Other diseases observed in the F3 generation include blindness, focal fat necrosis, interstitial pneumonia, liver degeneration, and cirrhosis. Many F1 and F3 females had an increase in ovarian cysts. F3 males demonstrated increased azoospermic and atretic seminiferous tubules, sloughed spermatogenic cells in the center of seminiferous tubules and absence of the seminiferous tubule lumen. Additionally, significantly greater exposed F3 males had higher spermatogenic cell apoptosis associated with reduced fertility. Tumors in the mammary glands, liver, and spleen were also observed in addition to increased incidence of obesity in F3 males[20]. Thus, in utero BPA exposure in rats leads to abnormal male and female reproductive system development associated with epigenetic alterations.

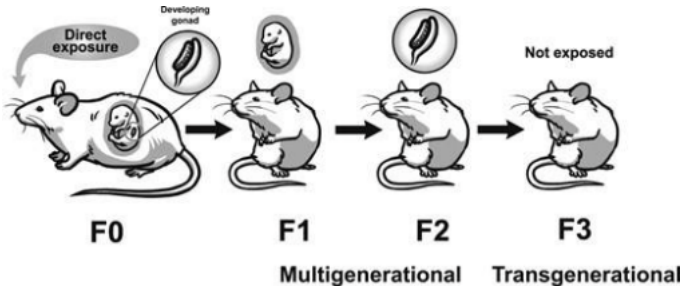

Figure 3. *In vivo* multi- and transgenerational inheritance of endocrine disrupting chemicals. Figured adapted from[21].

Mechanisms of Action of EDCs

EDCs induce epigenetic changes through DNA methylation, a process where a methyl group (consisting of one carbon atom bonded to three hydrogen atoms) is added to DNA cytosine bases via DNA methyltransferases. This modification alters gene activity without changing DNA sequences. For example, epigenetic changes caused by in utero exposure to BPA have multigenerational effects via methylation of imprinted genes (genes with an allele from one parent silenced) in the brain. Additionally, in a study conducted by Alavian-Ghavanini et al., prenatal BPA exposure to pregnant female rats causes epigenetic changes in the Grin2b gene in the immediate offspring, which is important for the regulation of neural morphology, memory, and learning[22]. DNA methylation by BPA has been found to affect neurodevelopment, as in utero exposure to BPA induces sex-specific methylation changes to estrogen receptors[23]. Another mechanism of inducing epigenetic change is through acetylation, which is where acetyl groups (consisting of a methyl group and a carbonyl group) are substituted for a hydrogen atom in a molecule. In the case of EDCs, lysine residues are acetylated, causing euchromatin formation resulting in increased transcriptional regulation[24]. Histone phosphorylation is another mechanism of epigenetic regulation, where phosphate groups are added to amino acids, serines, threonines, and tyrosines then to histones[25].

Two major developmental windows during which zygotes and fetuses are vulnerable to epigenetic changes from EDCs are early embryonic and germ cell development. During early embryonic development, the parental epigenome goes through drastic reprogramming after fertilization[26]. EDC exposure at this time can potentially disrupt this reprogramming or tamper with epigenetic marks, allowing for the transmission of unfavorable phenotypes across generations[27]. Fetal germ cells also undergo epigenetic reprogramming during their development, and changes that disrupt this reprogramming caused by EDCs are not corrected in successive generations. Thus, there exist diverse mechanisms promoting gene regulation via EDC exposure (**Fig. 4**).

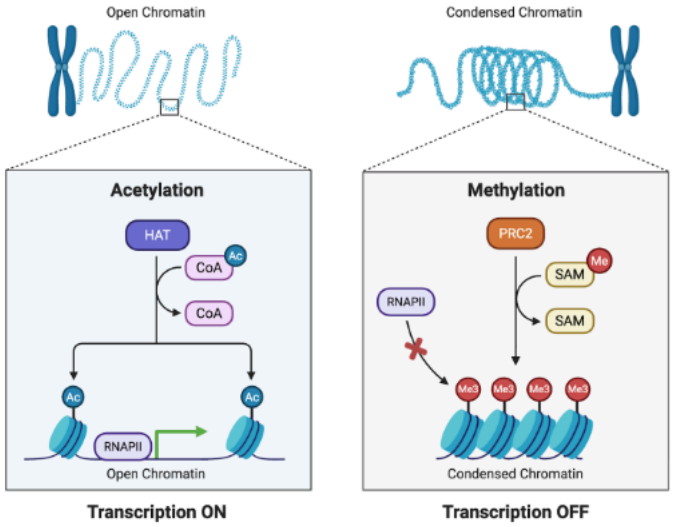

Figure 4. Direct and Indirection Transcriptional and Epigenetic Gene Regulatory Mechanisms. Image created using BioRender.

UNVEILING THE LIVER AS A TARGET FOR EDCS

Developmental and Physiological Origins of Liver Developement

The liver, in contrast to other organs, has a homogenous landscape of hepatocytes and consists of a liver lobule composed of plates of hepatocytes lined by sinusoidal capillaries that radiate toward a central efferent vein. Hepatocytes are a major functioning cell type in the liver and account for around 78% of liver volume. The basolateral surfaces on hepatocytes face fenestrated sinusoidal epithelial cells (specialized endothelial cells that line the capillaries of the liver) facilitating the transfer of endocrine secretions from the liver to the blood stream. Neighboring hepatocytes create small channels with collectible acids and salts. The complex arrangement between polarized hepatocytes, capillaries, and biliary epithelial cells, which are specialized cells that form the inner lining of ducts that transport bile, serve as the premise for endocrine and exocrine functions of the liver[28].

Before the liver fully matures, it undergoes multiple stages of development. The cardiac mesoderm, a crucial germ layer in the early embryo and a heart-forming region, plays a crucial role in hepatic cell development. Members of the fibroblast growth factor (FGF) family, a type of inductive signal, induce the onset of Albumin (an abundant protein found in the blood) expression. The main source of FGF during liver development is the endoderm. These signals, driven by FGF, facilitate liver cell specification. The Wnt signaling pathway, which is a network of proteins that enables cell communication and tissue morphogenesis, helps drive the specification, expansion, and differentiation of hepatocytes. Moreover, the mesoderm generates structures needed for the liver to form. Therefore, the coordinated embryologic origins of liver development are rooted in cell and tissue interactions of diverse germ layers[28]. A complex network of transcription factors controls the development of hepatoblasts, which are liver precursor cells.

For example, Hepatocyte Nuclear Factor 6 (HNF-6) and Prospero Homeobox 1 (Prox1) are transcription factors involved in the proliferation and subsequent migration of hepatoblasts. Moreover, T-box repressors, a family of transcription factors that repress the transcription of their target genes, promote hepatocyte fate and repress cholangiocyte fate[28]. Importantly, EDC exposure during critical periods of liver development is associated with liver disease progression and poses high risks for lipid accumulation. For example, EDC exposure in obese individuals is associated with lipid accumulation leading to steatosis, a reversible stage of NAFLD. Thus, EDC exposure may lead to aberrant liver development associated with varying stages of liver disease incidence and progression.

NAFLD, NASH, and Liver Cancer/Fibrosis as a Result of EDC Exposure

There exists an increasing amount of evidence suggesting that EDCs are metabolized in the liver. For example, phthalates—diesters of 1,2-benzenedicarboxylic acid used as industrial plasticizers—are EDCs commonly metabolized in the liver[6]. In humans, once phthalates are absorbed through inhalation or the skin, they are metabolized in the gastrointestinal tract and liver[29]. These processes are mediated by hepatic enzymes, such as Cytochrome P450 (CYP450), which metabolizes drugs and other foreign compounds. Phthalate metabolites can be found in the urine and are formed through enzymatic processes[30]. Phthalates are closely associated with metabolic diseases such as type 2 diabetes and obesity, which are also closely linked to the liver. For example, exposure to di-2-ethylhexyl phthalate (DEHP) in male quail disrupts lipid metabolism and induces liver inflammatory responses[31]. Moreover, higher urinary concentrations of DEHP have been shown to be positively correlated to NAFLD[32].

Phthalates are converted into their metabolites in two phases. First, phthalate diester parent compounds are hydrolyzed into mono-2-ethylhexyl phthalates (MEHP), with one ester bond broken. Lipases, which are enzymes that break down lipids, break ester bonds via hydrolysis and are crucial catalysts that split phthalate diesters into monoesters. This prepares the molecules for further processing in the second phase. In phase two, MEHPs become conjugated with glucuronic acid; this reaction is catalyzed by UDP-glucuronosyltransferases (UGTs) in the liver. Subsequently, CYP450 enzymes oxidize MEHPs further during or after conjugation. Glucuronidation increases metabolites' water solubility, allowing for their excretion in urine. This process also decreases their potential for endocrine disruption[32].

EDC exposure during stages of fetal development, puberty, and menopause increases the risk of NAFLD. As discussed, environmental disruptors may promote changes in gene expression and molecular processes, permanently changing the course of development and potentially inducing harmful effects later in life. For example, EDC-mediated epigenetic changes in liver development due to metabolic programming can lead to long-term hepatotoxic effects[33] and alter fetal liver phenotypes[34]. Studies indicate that phthalate exposure may enhance lipid accumulation in the liver and lead to lipid peroxidation, a process denoted by free radical-mediated attack phospholipids in cell membranes associated with inflammation in rats. Phthalates have caused oxidative stress within hepatocytes by inhibiting the JAK2/STAT5 pathway in BRL-3A fibroblasts, which could lead to NAFLD incidence[35].

EDC exposure can lead to a variety of metabolic disruptions causing NAFLD by blocking or mimicking natural hormones and hormone signaling pathways, including ones crucial for cellular metabolism. Many aspects of hormone regulation, such as production, release, transport, metabolism, binding, action, and elimination are interfered with by EDCs[36]. For example, mice exposed to low doses of the insecticides cypermethrin (CYP) and atrazine (ATZ) for 20 weeks caused increased levels of serum-free fatty acids (FFA), hepatic lipid accumulation and triacylglycerol (TG) levels. The de novo FFA synthesis pathway, which regulates fatty acid production, was altered due to aberrant gene regulation leading to increased mRNA levels[37]. Thus, fatty acid metabolism and fat storage were in imbalance due to metabolic dysregulation leading to NAFLD[38].

Additionally, NAFLD can lead to a cascade of more aggressive fatty liver diseases, such as NASH, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NAFLD begins as a simple benign hepatic steatosis denoted by fat accumulation in the liver[39]. Increased severity of NAFLD coupled with hepatic inflammation are characteristics of NASH[40]. NAFLD and NASH patients often present with hepatotoxicity caused by an increased flux of FFAs accompanied by endoplasmic reticulum (ER) stress in hepatocytes and linked to hepatic insulin resistance. In addition to stress and inflammation, numerous hepatocytes also undergo apoptosis. NASH is a risk factor for fibrosis progression, and around 40% of NASH patients experience fibrosis[40,41]. Meanwhile, progressive inflammation can lead to cirrhosis. Fatty liver diseases are now the second highest leading cause for cirrhosis, the first being alcohol related[40]. Excessive inflammation and cirrhosis can then lead to HCC, as 948,217 cases of HCC in western countries have been associated with NAFLD progression. Moreover, an additional meta-analysis demonstrated that NAFLD was independently associated with an 88% increased risk of HCC[39]. Thus, NAFLD associated with EDC exposure is linked to NASH, fibrosis, and possible HCC development (**Fig. 5**).

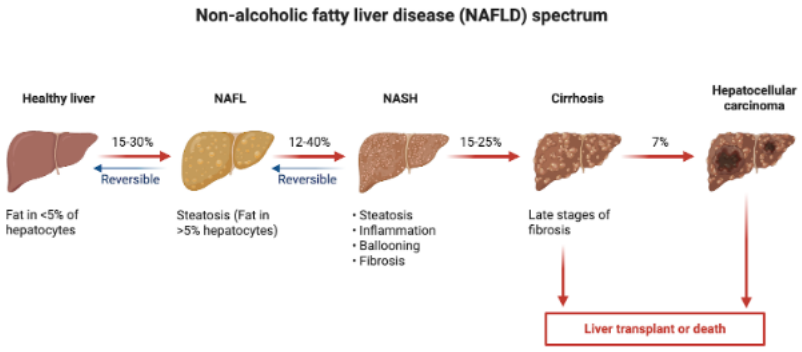

Fig. 5. Progressive Stages of Alcohol-independent Liver Diseases, Fibrosis and Carcinoma. Image created using BioRender.

Early intervention of NAFLD or NASH includes lifestyle modifications, even when diagnosed in advanced stages. Loss of greater than 10% body weight has been shown to reverse liver disease denoted by resolution of NASH symptoms and improvement of hepatic inflammation and fibrosis[42]. Dietary changes can also help improve liver function. For example, switching to a mediterranean diet that is high

in vegetables, legumes, whole grains, olive oil, fish, seafood, fruit and nuts and minimizes red and processed meats and sugar improves liver function and reduces risk of NAFLD. Therefore, modifications in lifestyle may also improve liver function and prognoses of liver-related diseases[43]. In a study evaluating the effects of caffeinated drinks on liver fibrosis in European patients, there is a negative association between regular coffee consumption and fibrosis[44]. Another study analyzing data from 782 adults demonstrated an inverse association between coffee intake and advanced fibrosis in NAFLD patients with high insulin sensitivity[45]. In patients with cirrhosis, treatments depend on the extent of liver damage.

Moreover, limiting alcohol use and losing weight can help slow its progression[46]. Pharmaceuticals can help prevent symptoms and complications. For example, lactulose may help with hepatic encephalopathy, a syndrome that can occur with cirrhosis, and terlipressin may relieve symptoms associated with hepatorenal syndrome, a complication of cirrhosis occurring in patients with severe liver disease[47]. In cases of NAFLD related HCC, liver transplants or resections are options for treatment. Ablation, which uses heat or other energy sources to kill tissue, transarterial chemoembolization, where high doses of chemotherapy drugs are directed to a tumor, and radiotherapy are other common options[48]. Thus, there exists a myriad of surgical and non-surgical methods to slow or completely remove risks associated with NAFLD, NASH, or NAFLD-related HCC.

DISCUSSION

In this paper, we discuss the impact of EDC usage in industrial, cosmetic, and agricultural industries on endocrine system function. Chemically, EDCs mimic natural hormones such as Estradiol and target their natural receptors. Subsequently, through interactions with their receptors, EDCs repress or activate genes through direct or indirect mechanisms, ultimately leading to changes in transcriptional regulation and protein activity. Exposure to EDCs in men and women can directly affect the genetic material present in sperm and unborn fetuses, respectively. These interactions cause permanent genetic or epigenetic changes that persist through multiple generations through direct targeting of DNA or through histone modifications (e.g. methylation, acetylation, and phosphorylation) to the epigenome. Moreover, indirect exposure to EDCs through interactions with germ cells present in developing fetuses, for example, can have devastating developmental effects that do not arise until adulthood. Critical developmental windows in zygotes and fetuses are times that make them vulnerable to the effects of EDC exposure. Importantly, EDC exposure can negatively impact organ formation, both in the paternal and maternal generations as well as indirectly exposed offspring. For example, EDC exposure to liver hepatocytes during critical developmental periods is associated with liver disease and fat accumulation later in life. Lipid accumulation over time can cause a cascade of effects ranging from NAFLD and NASH, to severe cirrhosis and HCC. Thus, limiting EDC exposure, especially during critical developmental periods or throughout pregnancy, may result in improved short and long term health outcomes. It is important to note that most of the current information concerning the effects of EDC exposure reviewed in this paper comes from in vivo and in vitro models which may not necessarily represent the same outcomes in humans. While the experimentally demonstrated mechanisms may be similar to those in humans, additional studies

need to be done to fully determine the implications of EDC exposure on human health, development, and reproduction.

Since fetuses and zygotes are most vulnerable to the effects of EDCs, it is crucial that pregnant mothers be protected from them in as many ways as possible. One step towards this is through increased governance of industrial manufacturers' practices. To ensure there are no health associated short or long-term health risks associated with EDC exposure, government-mandated third-party evaluation of the safety of EDCs, such as bisphenols, phthalates, heavy metals, and PFAS, in industrial manufacturing through rigorous experimental testing should be rendered. Moreover, similar evaluations should be conducted in cosmetic industries to limit the use of parabens and oxybenzone, which have been shown to induce damage to human health. The government can also enforce warning labels on manufactured products that contain EDCs, with a focus on products utilized by pregnant women. Furthermore, the government can allow the FDA to force companies to comply with human clinical trials to ensure products are safe to use prior to being mass produced. In addition to governmental restrictions on companies, hospitals can introduce more thorough testing procedures during pregnancy checkups to check for EDC exposure to the mother or the fetus. Doing so may aid in the clinical management of symptoms the patient or offspring is experiencing or may experience due to exposure. Collectively, this review has discussed EDC-related exposure on human health with a focus on liver development and disease and aims to highlight future efforts aimed at limiting the usage and mass production of products containing EDCs without providing rigorous evidence of their clinical safety. It is crucial to keep in mind, however, that further studies are needed to improve our understanding of how EDCs impact humans and how they behave inside the human body before any of the proposed policies and recommendations above are pushed forward.

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