Endocrine-disrupting Chemicals: Review of Toxicological Mechanisms Using Molecular Pathway Analysis

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Endocrine disruptors are known to cause harmful effects to humans through various exposure routes. These chemicals mainly appear to interfere with the endocrine or hormone systems. As importantly, numerous studies have demonstrated that the accumulation of endocrine disruptors can induce fatal disorders including obesity and cancer. Using diverse biological tools, the potential molecular mechanisms related to diseases by exposure of endocrine disruptors. Recently, pathway analysis, a bioinformatics tool, is being widely used to predict the potential mechanism or biological network of certain chemicals. In this review, we initially summarize the major molecular mechanisms involved in the induction of the above-mentioned diseases by endocrine disruptors. Additionally, we provide the potential markers and signaling mechanisms discovered via pathway analysis under exposure to representative endocrine disruptors, bisphenol, diethylhexylphthalate, and nonylphenol. The review emphasizes the importance of pathway analysis using bioinformatics to finding the specific mechanisms of toxic chemicals, including endocrine disruptors.

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Key Words: Endocrine disruptors, Molecular mechanism, Obesogen, Pathway analysis

INTRODUCTION

Endocrine disruptors are chemicals that interfere with the hormone systems and produce adverse developmental, reproductive, neurological, and immunological effects in mammals. Endocrine disruptors can be found in many products including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides. Although limited scientific information is available on the potential adverse human health effects, concern arises because endocrine disrupting chemicals present in the environment at very low levels have been shown to have adverse effects. Some research shows that these substances are also adversely affecting human health in similar ways, resulting in reduced fertility and increased progression of some diseases, including obesity, diabetes, endometriosis, and some cancers. These chemicals have also been referred to as endocrine modulators, environmental hormones, and endocrine active compounds. Because the hazards of endocrine disruptors are well known, a more complete study of the molecular mechanism is needed.

To analyze their different mechanisms, comprehensive analysis is required. As a typical comprehensive analysis in biology, pathway analysis can be efficient. Today, the quality and quantity of biological data are increasing. To process the large amount of data, a new field called bioinformatics has developed. Pathway analysis is one of bioinformatics tools whose goal is to identify the pathways significantly impacted. Pathway analysis has become the first choice for gaining insight into the underlying biology of genes and proteins that are differentially expressed. Through pathway analysis, researchers can find the direct
interactions, find the shortest paths, functionally group pathways, find the shortest pathway between selected genes/proteins, and find Primary/Secondary/Tertiary relationships. Finally, it can infer molecular mechanisms.

In this review, we summarize the known molecular mechanisms of endocrine disruptors focusing on cancer and obesity, and arrange the molecular mechanisms studies using pathway analysis focusing on bisphenol A (BPA), nonylphenol (NP), Di-(2-ethylhexyl) phthalate (DEHP) as representative endocrine disruptors.

EXPOSURE AND REGULATION OF ENDOCRINE DISRUPTORS

Food is the major route of exposure to endocrine disruptors (Fig. 1A). According to an article reported by Schecter et al., a total of 32 food samples from three major supermarket chains in Dallas were contaminated with polybrominated diphenyl esters (PBDEs). In this study, PBDEs are detected mainly in fish, meat, and dairy products. BPA exposure also occurs through diet, including contaminated food and water.5

The increase in household products containing pollutants and the decrease in building ventilation indoor air to become a significant source of endocrine disruptor exposure.4 In addition, endocrine disruptors accumulate from a variety of routes in the body (Fig. 1B).5 Phthalates are easily released into the environment and it is known that exposure of phthalates in the air induce asthma in children.0 NPs are produced industrially, naturally, and by the environmental degradation of alkylphenol...
ethoxylates. It originates principally from the degradation of NP ethoxylates which are widely used as industrial surfactants.  

Several environmental substances including heavy metals which seem to act as endocrine disruptors are reported. Numerous studies have demonstrated that tissues including kidney, liver and testis are sensitive to heavy metals toxicity. Heavy metals are released into the environments from industrial and agricultural products. Particularly, exposure through tobaccos is major source to human exposure with heavy metals.

With identifying evidence of the harmfulness of endocrine disruptors, their use is heavily restricted and the human body burden of the endocrine disruptors decline. The first step in reducing the body burden is eliminating or phasing out their production. The second step toward lowering human body burden is awareness of and labeling of foods that are likely to contain high amounts of endocrine disruptors. Endocrine disruptors were first discussed as a global issue at the ‘Rio summit’ in 1992. ‘Agenda 21’ was adopted at the summit and focuses on environmental safety management is of toxic and dangerous agents. Since that summit, endocrine disruptors have been regulated by various international organizations (Table 1). BPA has been controlled by restricting policy in countries around the world. This policy applies to World Health Organization as well as individual countries. The use of some phthalates has been restricted in the European Union (EU) since 1999 and in the United States since 2008. NP also is prohibited in the EU, the USA, and in other countries.  

### MOLECULAR MECHANISMS WITH ENDOCRINE DISRUPTORS

In general, endocrine disruptors are thought to affect an organism’s endocrine system. Additionally endocrine disruptors are known to affect other diseases such as cancer and obesity (Fig. 2). In the case of obesity, endocrine disruptors are called obesogens. This chapter deals with molecular mechanisms of endocrine disruptors already studied.

1. **Inhibition of endocrine receptors**

Endocrine disruptors can affect every level of the endocrine
Figure 2. Common molecular mechanisms of endocrine disruptors. (A) Endocrine disruptors act as receptors (especially endocrine receptor) binding inhibitors. Most harmful effects are initiated by this inhibition and is shown by most endocrine disruptors mechanism. (B) When the targets of endocrine disruptors were adipocyte, endocrine disruptors can be obesogens. In this case, peroxisome proliferator activated receptor (PPAR) on mesenchymal cells or progenitor cells are the targets. (C) In the case of cancer, endocrine disruptors act on the cell cycle. Cyclin protein and p21 protein were known to regulate cancer cells when exposed to endocrine disruptors. ER, estrogen receptor; MSC, mesenchymal stem cell. Cited from the article of Celik et al. (Chem Res Toxicol 2008;21:2195-206), Masuno et al. (Toxicol Sci 2005;84:319-27), and Ohtsubo et al. (Mol Cell Biol 1995;15:2612-24). 16-18

system. First, they can disrupt the action of enzymes involved in steroidogenesis. These enzymes can be inhibited, as can the enzymes involved in metabolism of estrogens. For instance, some polychlorinated biphenyl (PCB) metabolites inhibit sulfotransferase, resulting in an increase of circulating estradiol.19 The transport of hormones is also targeted by certain compounds capable of interacting with the binding sites of sex hormone binding globulin, thus competing with endogenous estrogens.20 The most studied mode of action of endocrine disruptors is their ability to bind and activate endocrine receptors (ERs) in target tissue. However, it is of note that the two ERs mediate distinct biological effects in many tissues, such as the mammary glands, bone, brain, and vascular system in both males and females. Therefore, because ERα and ERβ show different tissue distribution and distinct physiological functions, endocrine disruptors could display agonist or antagonist activity in a tissue-selective manner or during development. Considering the significant differences in structural features and relative ligand binding affinity of the ER subtypes, endocrine disruptors can induce distinct conformational changes in the tertiary structure of the ERs, affecting the recruitment of cofactors differently. These interactions between ERs and coactivators/corepressors are critical steps in ER-mediated transcriptional regulation and consequently the modulation of the expression of ER-target genes.

Moreover, the genistein effect is often tissue specific, depending on numerous factors such as the expression of specific cofactors, the ERα/ERβ ratio, and the level of expression of certain intracellular kinases, including cytoplasmic tyrosine kinases. Genistein has been reported to have both proliferative and anti-proliferative effects in cancer cells.21 Endocrine disruptors generally act in 100 to 1,000 folds greater concentrations than estradiol but can have additive or synergic effects with
endogenous estradiol or when they are present in combination. Furthermore, the ability of some endocrine disruptors to act as agonists in certain tissues and as antagonists in the others leads to the development and use of selective ER modulators, in particular for anti-hormonal treatments, such as tamoxifen and raloxifene. Some endocrine disruptors can also affect the ER non-genomic pathways and induce an endocrine disruption. For instance, a study performed on structurally different endocrine disruptors showed that at high concentrations, BPA and diethylstilbestrol are able to activate ERs via the activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase in breast cancer cells. In addition, the activation of protein kinase C (PKC) by some endocrine disruptors has been observed. Interestingly, PKC has been reported to modulate ERα transcriptional activity. Therefore, synergetic or additive effects between these pathways to combine the activation of ER signaling could be possible.

Cadmium is well known as an endocrine disruptor which affects the synthesis and/or regulation of several hormones. Indeed, cadmium affected progesterone synthesis in JC-410 porcine granulose cells and activated the ERα and/or mimic estrogen in different tissues (e.g., uterus and mammary gland) and breast cancer cell lines. Cadmium regulates androgen receptor gene expression and activity in LNCap cells, a hormone-dependent human prostate cancer cell line, and also mimics androgenic effects in rats and mice. In male rodents, it is well established that cadmium significantly alters the circulating levels of several hormones (e.g., testosterone, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]). Moreover it decreased steroidogenic acute regulatory protein, LH receptor and cyclic adenosine monophosphate (cAMP) levels in the testis. Cadmium affected the circadian pattern release of noradrenaline, a regulator of hypothalamus hormone secretion, which resulted in changes in the daily pattern of plasma testosterone and LH levels. In addition, plasma levels of pituitary hormones (e.g., LH, FSH, prolactin, and adrenocorticotropic hormone) were modified after cadmium exposure.

2. Obesity mechanism

Endocrine disruptors play another role in obesity and the metabolic programming of obesity risk. Their action predicts the existence of chemical obesogens, molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity. Although until now, data have been scant; some epidemiological and in vitro studies suggested a link between environmental chemical exposure and obesity.

The endocrine disruptors inducing obesity are called obesogens and have been reviewed. Obesogens have been shown to target transcription regulators found in gene networks that function to control intracellular lipid homeostasis as well as proliferation and differentiation of adipocytes. The major group of regulators that is targeted is a group of nuclear hormone receptors known as peroxisome proliferator activated receptors (PPARα, δ, and γ). These hormone receptors sense a variety of metabolic ligands, including lipophilic hormones, dietary fatty acids, and their metabolites, and, depending on the levels of these ligands, control transcription of genes involved in balancing the changes in lipid balance in the body. In order to become active and properly function as both metabolic sensors and transcription regulators, the PPAR receptors must heterodimerize with another receptor known as the 9-cis retinoic acid receptor (RXR). The RXR receptor, itself, is the second major target of obesogens next to the PPAR receptors. The central regulator in this process is the PPARγ, which associates with the RXR receptors and binds DNA targets as a heterodimer to directly regulate the expression at the transcriptional level. PPARγ is considered to be the master regulator of adipogenesis and plays key roles in nearly all aspects of adipocyte biology. It was recently proposed that PPARγ may function in adipogenesis without the need to be activated by a ligand. When the ligand binding domain of PPARγ was mutated such that the receptor was unresponsive to known agonists, the ability of preadipocytes to differentiate into adipocytes in cell culture was unaffected. The most reasonable interpretation of these data is that either PPARγ can act as an unliganded transcription factor to mediate adipogenesis, or that an as yet unknown endogenous ligand is being produced in response to the induction cocktail.

Notable among these are organotins such as tributyltin and triphenyltin and certain phthalates. Triorganotins and phthalates also have the ability to induce adipocyte differentiation in a variety of cell culture models. Other endocrine disruptors are known to promote adipogenesis, but probably do not act through PPARγ. These include BPA, organophosphate pesticides, monosodium glutamate, and PBDEs. PCBs bind the aryl hydrocarbon receptor in adipocytes and increase adipogenesis. BPA and alkylphenols stimulate adipogenesis in 3T3-L1 cells, and BPA diglycidyl ether was recently shown to induce adipogenesis in human and mouse bone marrow-derived mesenchymal stem cells. Although several endocrine disruptors are associated with adipogenesis and obesity in animal models, tributyltin is the only endocrine disruptor known to cause in
utero effects on adipocytes via activation of PPARγ. Prenatal exposure to tributyltin in mice led to a substantial increase in the amount of triglycerides in newborn tissues which normally have little to no fat at all. Although, the experiments did not distinguish whether more lipid was stored in existing cells, more cells were produced, or both. Other endocrine disruptors are likely to promote adipogenesis, in utero, although it is possible that this is secondary to broader metabolic imbalances. For instance, certain PCBs and PBDEs reduce thyroid function as does the antibacterial compound triclosan. The mechanisms of action are not completely certain, but possible modes include interference with thyroid hormone synthesis, transport, metabolism, or clearance.

3. Cancer mechanisms

Various studies have explored the role of endocrine disruptors in cancer. Breast cancer and prostate cancer are typical cancers caused by endocrine disruptors and compelling reasons to study endocrine disruptors. Despite various studies that have been completed, the direct roles of endocrine disruptors in cancer have not been clearly understood. Many researchers inferred that physiological unbalance created by endocrine disruptors might cause cancer. Generally endocrine disruptors are more harmful to woman than man and endometrial cancer and ovarian cancer are being researched.

Epidemiologic data on the effects of endocrine disruptors on endometrial cancer are limited. Researchers found no association between endometrial cancer and 27 PCB congeners, 4 dichlorodiphenyl-trichloroethane-related compounds, and 13 other organochlorine compounds. Several retrospective occupational cohort studies also observed no association. In the Seveso industrial accident, tetrachlorodibenzodioxin exposure appeared too small for a comprehensive evaluation.

There is some evidence that dietary isoflavones protect endometrial proliferation. Controversially, a randomized double-blind, placebo-controlled study on 298 post-menopausal women showed an increased incidence of endometrial hyperplasia following 5 years of treatment with 50 mg of soy isoflavones. Thus, phytoestrogenic supplements should be reconsidered, particularly in women at high risk for endometrial cancer. Isoflavones are known as beneficial materials but they can be harmful to the body because these are actually endocrine disruptors.

Ovarian function is controlled by the hypothalamus, pituitary, and auto-paracrine factors. Hormone-mimicking compounds can bind to cell receptors, interfere with hormone action, and affect ovarian function. It is not clear how endocrine disruptors affect ovarian function, but a disruption in gonadotropin (i.e., FSH and LH) secretion and feedback mechanisms involving estradiol (E2) and progesterone (P4) may be involved.

Alternatively, endocrine disruptors may affect ovarian hormone production and oocyte maturation. Damaged oocytes can affect overall hormone production and follicular function, resulting in an endocrinological imbalance (i.e., a decrease in E2 and P4, but an increase in FSH and LH) and ovarian failure. Ovarian cancer is the most prevalent type of gynecological cancer affecting women residing in Western countries. As more than 60% of tumors are diagnosed at stage III and certain forms of cancer are very aggressive, ovarian cancers are associated with a high mortality. While most cells undergo neoplastic transformation, including germ cells, granulose, and stromal cells, approximately 90% of tumors are derived from the ovarian surface epithelium. Similar to breast cancer, hormonal factors such as estrogen and xenoestrogens have been linked to ovarian cancer. However, the role of environmental toxins in ovarian cancer requires further study.

**DISCOVERY OF MOLECULAR MECHANISMS BY ENDOCRINE DISRUPTORS EXPOSURE USING PATHWAY ANALYSIS**

The biological pathways and processes that occur in a tissue are reflected in the gene expression profile of that tissue. Alterations in gene expression upon chemical exposure may result in phenotypic changes that relate to the mode of action of that chemical and any associated toxicity. The ability to determine which Gene Ontology terms and biological pathways are associated with differentially expressed genes from a microarray experiment, which we call gene ontology or pathway mapping, would therefore be an ideal way to gain an understanding of the molecular processes affected by the gene expression changes and so reveal information on mode of action and toxicity. Recently, many groups have developed methods and tools for pathway and gene ontology mapping that reveal statistically significant annotations associated with microarray data. In addition, several recent publications have used gene ontology to aid the interpretation of toxicogenomic data.

Three chemicals are focused on in this review: BPA, NP, and DEHP (Fig. 3). These chemicals are typical endocrine disruptors and also the numbers of studies are the most
Figure 3. The related pathway of molecular/cellular process and disease/disorder. (A) Bisphenol A. Included molecular/cellular process and diseases/disorders were collected from the relevant papers.57-60 (B) Phthalate. Included molecular/cellular process and diseases/disorders were collected from the relevant papers.61-75 (C) Nonylphenol. Included molecular/cellular process and diseases/disorders were collected from the relevant papers.76-82 Each pathway was discovered using pathway analysis. Researchers can find the significant molecular and cellular pathway and compare and infer the correlation between the endocrine disruptors and the disease in terms of gene ontology. The pathway analysis can open up the possibility for more study. LEF1, lymphoid enhancer-binding factor 1; PPAR, proliferator activated receptor; ICF3, immunodeficiency-centromeric instability-facial anomalies syndrome 1.
abundant. In fact, some government agencies take these three chemicals as representative substances of all the endocrine disruptors. Researches show these chemicals can disrupt reproductive and developmental systems, increase cancer risks and damage the immune systems of experimental laboratory animals.85

1. Bisphenol A

BPA is a carbon-based synthetic compound with the chemical formula \((\text{CH}_3)_2\text{C}((\text{C}_6\text{H}_4\text{OH})_2\)). with two hydroxyphenyl groups belonging to the group of diphenylmethane derivatives and isophenols. It is a colorless solid that is soluble in organic solvents, but poorly soluble in water and has been in commercial use since 1957. A 2010 report from US Food and Drug Administration identified possible hazards to fetuses, infants, and young children.86 The major human exposure route to BPA is diet, including ingestion of contaminated food and water.3 BPA is leached from the lining of food and beverage cans, where it is used as an ingredient in the plastic used to protect the food from direct contact with the can.87 BPA can enter the environment either directly from chemical, plastic coating, and staining manufacturers, from paper or material recycling companies, foundries who use BPA in casting sand, or indirectly leaching from plastic, paper, and metal waste in landfills or ocean-borne plastic trash.

BPA is an endocrine disruptor that can mimic estrogen and has been shown to cause negative health effects in animal studies. Early developmental stages appear most sensitive to its effects, and some studies have linked prenatal exposure to later physical and neurological effects.88 BPA has been proposed to increase the risk of obesity, brain diseases, disruption of the hormone system/reproduction system, cancer, asthma, and heart disease.89

A few groups have used microarrays for in vivo studies of the effects of BPA exposure. Saili et al.77 studied the effects of BPA exposure in the development of zebrafish. They identified 26-genes affected by exposure to BPA and reported that those genes were related to the cAMP response element. Lam et al.58 also studied zebrafish to see the effects of BPA exposure, but focused on phenotype analysis. They defined 38-genes to suggest dose-dependent effects following BPA exposure and detected those genes involved in 11-molecular mechanisms. In vitro studies of BPA exposure followed. Yin et al.95 studied human embryonic kidney cells exposed to BPA. They identified 8-up-regulated genes and 7-down-regulated genes significantly differentially expressed after BPA exposure. They confirmed that there were 15 molecular mechanisms acting. Qin et al.50 studied BPA exposure with human foreskin fibroblast cells from hypospadias patients. Hypospadias is one of the most common congenital abnormality with a global prevalence of approximately 0.2% to 1.0% at birth in male infants. They identified 29-up-regulated genes and 42-down-regulated genes after BPA exposure, suggesting related functions in response to BPA. They also constituted 5 groups of molecular mechanisms associated with those genes.

2. Di-(2-ethylhexyl) phthalate (phthalate category)

DEHP is an organic compound with the formula \(\text{C}_6\text{H}_4\text{(CH}_3\text{C}_4\text{H}_9\text{COO})_2\)). It is the diester of phthalic acid and the branched-chain 2-ethylhexanol. Generally it has suitable properties and low cost DEHP is widely used as the plasticizer in manufacturing of articles made of Polyvinyl Chloride (PVC).90 Three billion kilograms are produced annually worldwide and its environmental exposure has been issue. It can be absorbed from food and water, with higher levels found in milk and cheese.91

DEHP is known as a potential endocrine disruptor, which can affect development, obesity, and cardiotoxicity.90 In general, the exposure of children to phthalates is greater than for adults because infants’ and toddlers’ mouthing behavior.91 For that reason much of current research on the effects of phthalate exposure has been focused on children’s health.92 The relationship between obesity and endocrine disruption is a current issue. Phthalate metabolites showed statistically significant correlations with obesity and insulin resistance.93

The studies of pathway analysis with phthalate have mainly focused on the testis. Other studies have been conducted on in cancer cell lines and cardiac muscle cells. The focus on the testis is phthalate inhibits the action of testosterone as an endocrine disruptor.94 In the present study, 21 pathways were shown to change significantly due to phthalate exposure in testis.95-100 PPAR signaling pathway and p53 signaling pathway are among the 21 pathways as representative molecular mechanisms. A total of five genes consistently show to significant response to phthalate in several studies.61-66 The five genes are involved in steroid metabolism, and genes such as those may be an indicator of phthalate exposure. In other studies, cardiac muscle have been studied that associate cardiovascular disease with phthalate. The PPARα is one common gene that significant changes in response to phthalate in cardiac muscle.96 PPARα is a key regulator of lipid metabolism and a peroxisome proliferator.67 In fact, a lot of research on diseases, including cardiovascular disease, have been reported due to oxidative stress caused by phthalate.68,90 in vitro tests, pathway analysis is being conducted. In testicular
carcinoma cells treated with phthalate, three genes (GJA1, CLDN6, MMP2) were changed significant. GJA1 was significantly down regulated and CLDN6, MMP2 were significantly up regulated. It is known that all three genes, performing functions related to cell interaction. Several studies have been associated with disease and the above genes. Additional studies are required to study these genes. Pathway analysis related to phthalate has been studied in breast cancer cells as well as other cancers. When compared to the known existing cancer study. lymphoid enhancer-binding factor 1 (LEF1) is the most significant gene. LEF1 is well known to participate in the Wnt signaling pathway and may play a role in hair cell differentiation and follicle morphogenesis. Generally known to be found in normal thymus. it is found highly expressed in several cancer biopsy and cell lines. LEF1 might be a new indicator of cancer from phthalate exposure.

3. Nonylphenol

NPs are a family of closely related organic compounds called alkylphenols. They are used in manufacturing antioxidants, lubricating oil additives, laundry and dish detergents, emulsifiers, and solubilizers. These compounds are also precursors to the commercially important non-ionic surfactants alkylphenol ethoxylates and nonylphenol ethoxylates, which are used in detergents, paints, pesticides, personal care products, and plastics. NP has attracted attention due to its prevalence in the environment and its potential roles as an endocrine disruptor and xenoestrogen, due to its ability to act with estrogen-like activity. NPs act as xenoestrogen like endocrine disruptors by binding to estrogen receptors and competitively inhibiting natural estrogens. NPs have been shown to mimic the natural hormone 17β-estradiol and to compete with the endogenous hormone for binding with estrogen receptors ERα and ERβ.

Unlike other endocrine disruptors, pathway analyses with NPs are lacking. Pathway analysis with nonylphenol has been studied in the seminiferous tubule, because NP is known to act on the testis. Pathway analysis was also studied in the immune system. In the present study, the researcher looked at the change of expression with DNMT3 (DNAcytosine-5-methyltransferase3) gene. DNMT3 is required for genome-wide de novo methylation and is known to be essential for the establishment of DNA methylation patterns during development. A representative disease associated with DNMT3 is immunodeficiency-centromeric instability-facial anomalies syndrome 1 (ICF3) where studies show limited hypomethylation of DNA in a small fraction of the genome in some patients. Another study about pathway analysis with NPs is focused on the change of miRNAs expression. They analyzed the miRNAs level changes in mouse testis exposed to NP, tracking the targets of miRNAs. Two genes (CCNE1, peroxisome proliferator-activated receptor α [PPARA]) showed associated change with miRNAs. In the CCNE1 (G1/S-specific cyclin-E1) case, the related disease is not known yet, but is known as an essential factor of the cell cycle at the G1/S (start) transition. The PPARα gene is known as a key regulator of lipid metabolism and as a ligand-activated transcription factor. They also focused on one miRNA that was the most significantly changed, and analyzed the target genes of miRNA. Twenty genes were classified and those genes were related to cell cycle, cell death, cell morphology, cell-to-cell interaction/signaling and cellular assembly and organization.

DISCUSSION

Today, there are various diseases of unknown cause which endocrine disruptor has been implicated and research is needed. To measure and analyze hazardous materials is important. But it is difficult to define the molecular mechanisms that hazardous materials. In the case of endocrine disruptors which have various mechanisms, the process can be difficult. We have summarized the effects of endocrine disruptors and classified them into three classes: hormone disrupting, obesity related, and cancer related. With this classification, their molecular mechanisms are also identified. But the identified mechanisms were only general and do not cover all the specific mechanisms of endocrine disruptors.

Bioinformatics can provide efficient methods to analyze and find molecular pathway. Indeed some researchers executed pathway analysis with endocrine disruptors and we looked at these in this review. Pathway analysis in bioinformatics can be applied under various conditions, but we only focused on the material condition. Because bioinformatics tools analyze experimental results, if pathway analysis have accessed other conditions researchers can get other results.

The ER signaling pathway and the PPAR signaling pathway are affected by endocrine disruptor. We can see two mechanisms in pathway analysis focused on material condition. However we can also propose other molecular mechanisms from pathway analysis. Researchers can study the disease in terms of different mechanisms other than the known mechanism. Pathway analysis not only shows various mechanisms of hormone disrupting, obesity and cancer, but also suggests other disorders and diseases related endocrine disruptors. If they parallel with experiments and bioinformatics tools, the direction of study on endocrine...
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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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