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Review Paper: Endocrine-Disrupting Chemicals Role in Drug Abuser: A Review Study

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ABSTRACT

Endocrine-disrupting Chemicals (EDCs) are exogenous chemicals that influence many aspects of natural hormone actions. Bisphenol is used in the industry, for increasing the thickness and durability of materials in certain plastics and resins. Paraben is used as preservatives in many pharmaceuticals, cosmetics, and some food products. EDCs can increase estrogen levels inside the body, and estrogen itself can increase the monoamine effect (dopamine, serotonin), neuronal excitability, neuropeptide transmitter mechanism, and drug metabolism. In drug abusers, this effect can develop greater craving behavior, addiction, and relapse.

1. Introduction

The modern-day environment is filled with thousands of synthetic chemicals and compounds used in everyday life. These chemicals are found in the environment and most of them are used by humans. Some of these chemicals are useful and beneficial to the human body while numerous other chemicals were toxic and can cause undesirable effects. Exposure to these chemicals can be through various ways and the effects can range from minor or trace to carcinogenic. Developing countries like Malaysia are among the highest users of various types of man-made chemicals in a large number of consumer products, such as cosmetics, soaps, shampoos, electronic gadgets, textile, perfumes, paints, fertilizers, and pesticides. The development in the industry has caused a negative impact on the environment. Each year numerous new compounds with unknown effects on human health are being created and eventually found their way into the environment. These contaminations have caused public concerns that man-made chemicals might give negative health effects on the population. Many of these synthetic chemicals possess estrogenic activity and have been classified as endocrine-disrupting chemicals (EDCs) [1].

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Multiple research studies have connected EDCs to cancer, diabetes, obesity, and infertility in humans [1-3]. EDCs can block, mimic, or modulate the synthesis, release, transport, metabolism, and binding or elimination of natural hormones. Therefore, any disruption in this system will cause an abnormal function or development in the reproductive, nervous, and immune systems. EDCs may generate a harmful effect even if they are present in the environment at very low or trace levels [4]. Exposures to known EDCs are relatively high in contaminated environments. Industrial chemicals can leak into soil and water. Then, they are consumed by microorganisms, algae, and plants.

Animals eat plants, and bigger animals eat smaller ones. Accordingly, animals at the top of the food chain, including humans, have the highest concentrations of such environmental chemicals in their tissues. EDCs include polycarbonate by-products, surfactants such as octylphenol, insecticides such as dichlorodiphenyltrichloroethane (DDT) and its metabolites, endosulfan, phthalate, polychlorinated biphenyls (PCBs), dioxins, alkylphenols (APs), bisphenol, parabens, pesticides, and polycyclic aromatic hydrocarbons (PAHs) [1, 2, 5, 6].

2. Review of EDCs

2.1. Bisphenol

2.1.1. Properties

Bisphenol (Figure 1) is an industrial chemical that has been used to make certain plastics and resins since the 1960s. It is used in the industry for increasing the thickness and durability of materials. Bisphenol is frequently used in polycarbonate plastic, food storage containers, reusable drink containers, children's toys, and canned foods. It is released from consumer goods, leading to its detection in wastewater, drinking water, soil, dust, food, and air. Bisphenol A (BPA's) global annual output is approximately 6.8 million tonnes [7-10].

Polycarbonate plastic is used to make sports equipment, CDs, DVDs, baby and water bottles, foundry castings, medical, and dental devices, household electronics, eyeglass lenses, and water pipes lining [2, 11, 12]. Bisphenol A (BPA,), Bisphenol B (BPB,), Bisphenol S (BPS,), Bisphenol F (BPF,), and Bisphenol AF (BPAF) were studied in this research (Table 1). Bisphenols are mostly soluble in ethanol, acetone, methanol, benzene, chloroform, and ether [12-14].

2.1.2. Pharmacology

In the workplace, in which bisphenol products are produced, inhalation and dermal exposures are the most probable routes of toxicity. While in the general population, major exposure to bisphenol is via the oral route (ingestion of contaminated food and water) [15-19]. Some foods and water are stored in food cans, which are lined with BPA epoxy resin films. In the pediatric population (infants and children), milk and beverage bottles provide daily exposure to BPA [7, 20]. Bisphenol A in human volunteers is absorbed rapidly via the gastrointestinal tract. Metabolism is performed in the liver with a rapid conjugation process with UDP-glucuronic acid, forming BPAG (BPA glucuronide). BPA glucuronide is rapidly formed and excreted via urine, feces, or bile, with a half-life of about 5.3 hours. All of these processes are complete within 24 hours [21]. The fetus and newborn can receive BPA from the mother via placental transfer and milk. One study showed that BPA could be detected in sweat and induced sweating is a clinically useful method to eliminate BPA from the body [22].

2.1.3. Toxicity

BPA similar to endogenous estrogen which can bind with estrogen receptors, stimulate estrogen production, and also alter gonadotropin hormone secretion [23, 24]. These mechanisms can stimulate endometriosis formation. Some studies found the association of urinary BPA concentrations with semen quality. In male Chinese workers, who were highly exposed to BPA (median urinary BPA concentration =38.7 ug/L), sperm concentration, total count, and activity had reduced [7, 16, 17]. Research in men partners of the infertile couple showed a positive correlation between BPA level in urine and abnormal sperm morphology [25].

In 84 women undergoing treatment with InVitro Fertilization (IVF), a reported correlation is seen between BPA level in urine (median =2.6 ug/L) with reduced oocyte yield and peak serum estradiol [26-28]. One cross-sectional study on 192 female teenagers showed a possible association between later onset of breast development and higher urinary BPA level [29, 30]. Another research was held in the third trimester of 367 pregnant women that had 1.3 µg/L urinary BPA concentration. There was a modest elevation in neonatal birth weight [30]. While cohort study in 249 pregnant women (with 2.0 µg/L urinary BPA concentration) had a positive association with children externalizing behaviors (such as aggression and hyperactivity) using the behavioral assessment system for children-2 (BASC-2) [31-33].

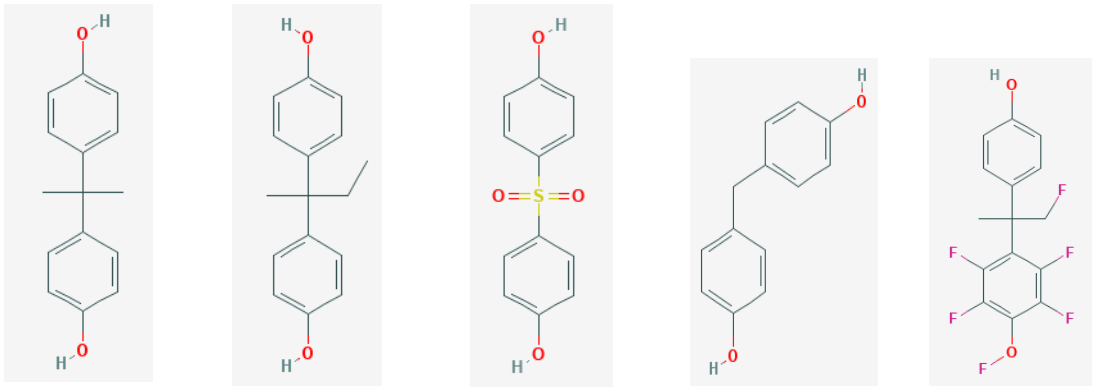

Figure 1. Structure of bisphenols

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2.1.4. Biologic monitoring

For bisphenol human biologic monitoring, some studies used various matrices such as placental tissue, urine, serum, semen, blood, amniotic fluid, breast milk, follicular fluid, and umbilical cord blood (Table 2). Bisphenol A can pass the maternal-fetal placental barrier, so mother and baby serum, amniotic fluid, cord blood, and placental detection suggest the risk of fetal exposure to Bisphenol A [34, 35]. Analytical techniques applied for measuring bisphenol in the human matrix are GC-MS, LC-MS, LC-MS/MS, and enzyme-linked immunosorbent assay. Glucuronidase treatment for urine is important to do for releasing glucuronic acid conjugation, then extracted by SPE, LLE, stir bar sorptive extraction, and SPME [6, 36].

2.2. Paraben

2.2.1. Properties

One of the groups of alkyl esters of the p-hydroxybenzoic acid, broadly used as preservatives in pharmaceutical, food, and personal care products are called parabens. This group includes methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben. Methylparaben, ethylparaben, propylparaben, and butylparaben were studied in this research (Figure 2). These chemicals have simple esters with effective antimicrobial and antifungal properties. Although they have low toxicity, parabens belong to EDCs [39]. Products found to contain parabens include hand soap, body lotion, shampoo, conditioner, cosmetics, hair spray, toothpaste, jams, jellies, fillings, and toppings [40]. In the environment, parabens are detected in urban streams, rivers, and drinking water sources [41].

Table 1. Properties of bisphenols

No.	Compound	Physical Description	Color	Odor	Boiling Point	Melting Point
1	BPA 2,2-Bis (4-hydroxyphenyl) Propane	Dry powder, liquid, other solid, pellets large crystal.	White flakes to cream	Mild phenolic odor	360.5°C	153°C
2	BPB 2,2-Bis (4-hydroxyphenyl) butane	Crystal, dry powder	Crystal or tan granule	Mild odor	120.5°C	125°C-127°C
3	BPS Bis(4-hydroxyphenyl) Sulfone	Dry powder	White crystalline powder	Mild odor	505°C	240.5°C
4	BPF Bis(4-hydroxyphenyl) methane	Dry powder	White	Mild odor	390°C	162.5°C
5	BPAF 2,2-Bis(4-hydroxyphenyl) hexafluoropropane	Tan coarse powder	White, light gray	Mild odor	400°C	161°C

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Table 2. Analysis of bisphenol in human biological samples using LC-MS/MS

No.	Analyte	Sensitivity	Sample	Preparation	References
1	BPA	LOQ: 0.1 ng/mL	Urine	SPE	[7]
2	BPA	LOQ: 15 µg/L	Urine Plasma	Protein precipitation	[21]
3	BPA	LOQ: 0.05 ng/mL	Blood Urine	Protein precipitation (for blood) SPE (for urine)	[37]
4	BPS	LOQ: 0.02 ng/mL	Urine	SPE	[38]
5	BPA and analogs	LOD: 0.04-6.4 ng/mL	Urine Cord blood	LLE	[24]

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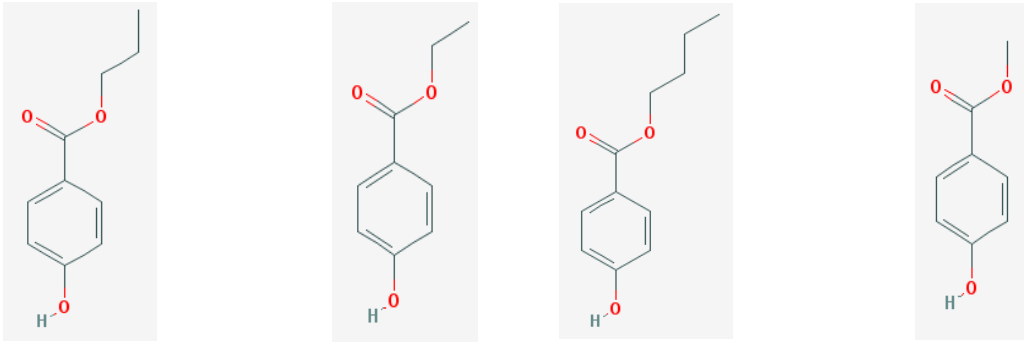
Parabens are odorless, tasteless, or numbs the tongue; they are mostly soluble in ethanol, water, methanol, acetone, and ether (Table 3). They are stable under the hydrolysis process during autoclaving and resist saponification. Methylparaben is an antimicrobial, a neuroprotective, and an antifungal agent found naturally in several fruits. Ethylparaben is found in alcoholic beverages, such as white wine, red wine, and sake. Butylparaben and propylparaben are flavoring agents and chemical allergen that promote histamine release. The exposure via food is because of their natural occurrence, their use as a preservative, and leakage from food packaging material [39, 42].

2.2.2. Pharmacology

The main route of exposure to parabens is via oral and skin penetration. Parabens are rapidly metabolized by the liver (through esterase hydrolysis and glucuronidation by several UGT isoforms), plasma, and in the skin. The hydrolysis in human liver microsomes is conducted more rapidly than in plasma. Then they are converted into p-hydroxybenzoic acid, followed by excretion via urine. They are commonly excreted as glucuronide conjugates, sulfate, and glycine. Paraben glucuronides are more specific compared to 4-hydroxybenzoic acid and have been used as urinary biomarkers of parabens exposure in humans. Personal care products contributes more blood paraben than oral. It is because, in oral exposure, there is fast metabolism conducted by the intestine and liver [42]. Methylparaben and ethylparaben (95%) are more stable in human plasma compared to propylparaben, butylparaben, and benzylparaben (50%) after 24 hours. Parabens are substrates of UGT1A8, UGT2B7, UGT1A9, UGT1A1, UGT2B17, and UGT2B15 (UDP-glucuronosyltransferase isoforms) [46].

2.2.3. Toxicity

Parabens have estrogenic activity because they can bind to estrogen receptors. This mechanism might exert a hormonal impact on the body. They can inhibit an estrogen-inactivating enzyme (17β-hydroxysteroid dehydrogenase) [42]. A study showed that high urinary BPA and butylparaben levels are associated with higher sperm DNA damage (P=0.03) [25]. At the cellular level, there are some reports that parabens can disrupt cellular function and cause chromosomal aberration. Parabens belong to lipophilic pollutants that are known to



Propylparaben Ethylparaben Butylparaben Methylparaben

Figure 2. Structure of parabens

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Table 3. Properties of parabens

No.	Compound	Physical Description	Color	Odor	Boiling Point	Melting Point
1	Propylparaben	Crystals or powder	Colorless, white powder or chunky white solid	Odorless or mild phenolic odor	271°F	95°C-98°C
2	Ethylparaben	Crystals or powder	Colorless crystals or white powder	Odorless	297°C-298°C	213°C-217°C
3	Butylparaben	Small crystals or powder	Colorless crystals or powder	Odorless	156°C-157°C	68.5°C
4	Methylparaben	Small crystals or powder	Colorless crystals or powder	Odorless or faint odor	275°C	131°C

Table 4. Analysis of paraben in human biological samples using LC-MS/MS

No.	Analyte	Sensitivity	Sample	Preparation	References
1	Methylparaben, ethylparaben, n-propylparaben, n-butylparaben, isobutylparaben	LOQ: 10 ng/g	Breast tissue	LLE	[11]
2	Methylparaben, ethylparaben, propylparaben butylparaben, BPA	LOD MP: 1.0 µg/L; PP and BP: 0.2 µg/L	Urine	SPE	[25, 47]
3	Methylparaben, ethylparaben, n-propylparaben, butylparaben, benzylparaben	LOD MP: 0.13; ng/mL; PP: 0.18 ng/mL, and others: 0.10 ng/mL	Urine	SPE	[43]
4	Methylparaben, propylparaben, benzylparaben	LOQ: 20 ng/mL	Blood	SPE	[49]

MP: Methylparaben, PP: Propylparaben, BP: Butylparaben.

bioaccumulate in fatty tissue. They can be accumulated in human breast tumors, with a mean concentration of 20.6±4.2 ng/g tissue [40]. Besides, a study on more than 1800 US people reported inverse associations between parabens concentration and circulating thyroid hormone levels in adults, mainly in females [47].

2.2.4. Biologic monitoring

There are several issues about the effect of long-term parabens exposure to the human body, leading to much research that detect paraben level in human samples. The human samples that can be used to detect parabens are tumor tissue, blood, human milk, seminal plasma, breast

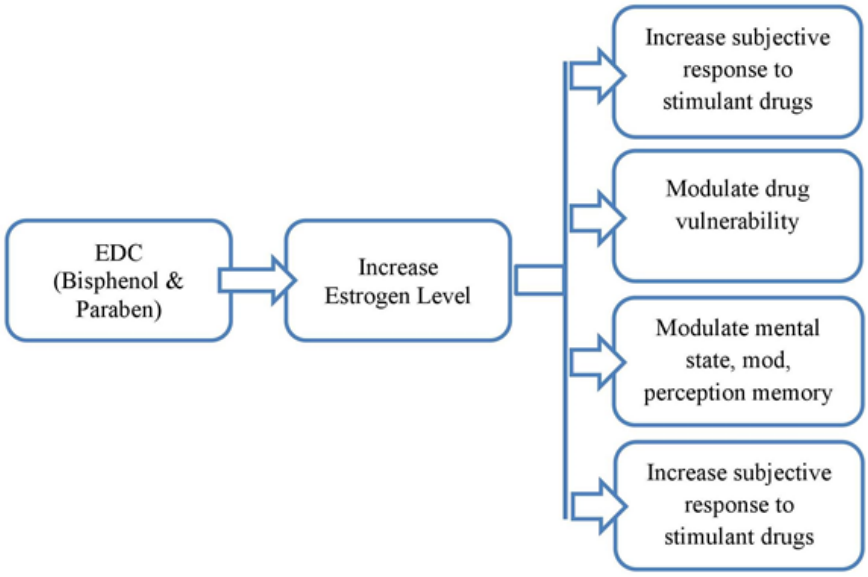

Figure 3. The Role of EDC

tissue, placental tissue, saliva, and urine (Table 4). Extraction and purification strategies (to disrupt the protein-compound binding and facilitate) are LLE, dispersive LLE, stir-bar sorptive extraction, supercritical extraction, solvent extraction, protein precipitation, SPE, and SPME. The analytical methods most commonly used for the determination of biomarkers or paraben exposure are LC-MS/MS and GC-MS [48]. Samples in the pediatric patient are collected because pediatric liquid formulations contain excipients such as methylparaben and propylparaben [49].

3. The Role of EDCs in drug abuse

There is a strong association between hormonal factors and drug metabolism. EDCs can enhance estrogen levels in the body, and estrogen can increase the monoamine effect (dopamine, serotonin), neuronal excitability, neuropeptide transmitter mechanism, and drug metabolism. This mechanism can modulate mental state, mood, perception, behavior, memory, and drug vulnerability [50]. Some drug metabolism is faster in women than in men, so with the same dosage, it may exert different effects on men and women. The increase in dopamine can develop greater craving behavior, addiction, and relapse in drug abusers. Women have greater craving behavior in response to nicotine and cocaine, then more likely to relapse during and after the treatment, and have shorter abstinence periods after cocaine treatment, compared to men. Besides, estrogen may increase subjective response to stimulant drugs and accordingly increase craving behavior (Figure 3) [51].

4. Conclusion

Broadening our knowledge of the effects of bisphenol and parabens can increase the estrogen level. Increasing estrogen levels can influence the behavior, treatment, and prognosis of a drug addict. EDCs level in drug abusers is a challenging study to know the exposure of EDCs in the selected population, especially in a drug abuser.

Ethical Considerations

Compliance with ethical guidelines

Institutional approval for the analysis of human samples was obtained from the Ethical Committee of University Malaya Medical Centre

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Author's contributions

Visualization, Writing – review & editing: All authors; Supervision: Mustafa Ali Mohd, Rusdi bin Abd Rashid, Didi Erwandi bin Mohamad Haron; Investigation, Methodology, Resources, ROLES Conceptualization: Idha Arfianti Wiraagni, Mustafa Ali Mohd, Didi Erwandi bin Mohamad Haron; Data curation, Formal analysis, Software, Validation: Idha Arfianti Wiraagni, Didi Erwandi bin Mohamad Haron; ROLES Methodology: Rusdi bin Abd Rashid; Funding acquisition, Project administration: Idha Arfianti Wiraagni.

Conflict of interest

The authors declared no conflict of interests.

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