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Physiological Effects of Plastic Wastes on the Endocrine System (Bisphenol A, Phthalates, Bisphenol S, PBDEs, TBBPA)

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Abstract: The research evaluated the association between plastics and endocrine disruptors, as well as the viable and active ways to mitigate the challenges posed by plastic pollution. Consumption of seafood represents one major pathway for the exposure of human to microplastic. Microplastics may pass up to higher levels in food chain. Three likely toxic effects of plastic particles have been put forward: the release of persistent organic pollutants (POPs) adsorbed to the plastics, leaching of plastic additives, and plastic particles themselves. Chemical additives such as bisphenol A (BPA), phthalates, polybrominated diphenyl ethers (PBDE), tetrabromobisphenol A (TBBPA), bisphenol S (BPS), etc., used in plastic production pose several health risks to both humans and animals. Due to the use of some chemical additives during production of plastics, plastics have potentially risk and harmful effects that could be carcinogenic or encourage endocrine disruption. Some of the chemical additives are used as phthalate plasticizers (phthalates) and brominated flame retardants. By biomonitoring, chemicals in plastics, such as phthalates and BPA, have been identified in human population. Humans are exposed to the chemicals through the skin, nose, or mouth. Bisphenol A (BPA) can disrupt normal, regular physiological levels of sex hormones. Recent studies suggest that BPS also has endocrine disrupting properties, just like BPA. The presence of a hydroxy group on the benzene ring makes bisphenol S and bisphenol A endocrine disruptors. A widespread concern about phthalate exposure is the possibility that it is the cause of a drop in male fertility. Some recent studies suggest that tetrabromobisphenol A may be an endocrine disruptor and immunotoxicant. As an endocrine disruptor, tetrabromobisphenol A may interfere with both estrogens and androgens. There is also growing concern that PBDEs share the environmental long life and bioaccumulation properties of polychlorinated dibenzodioxins. It is not known if PBDEs can cause cancer in people, although liver tumors developed in rats and mice that ate extremely large amounts of decaBDE throughout their lifetime. The use of biodegradable plastics, policymaking, institutional arrangements, plastic waste collection, promotion of non-usage and lessening usage, incineration, use of the enzyme PETase, and creating awareness, in addition to banning have been the active ways for the management of plastic pollution.

Keywords: Plastic Wastes, Endocrine Disruptors, Bisphenol A, Phthalates, Bisphenol S, PBDEs, TBBPA, Microplastics

1. Introduction

Due to the use of some chemical additives during production of plastics, plastics have potentially risk and harmful effects that could be carcinogenic or encourage endocrine disruption. Some of the chemical additives are used as phthalate plasticizers (phthalates) and brominated flame retardants. By biomonitoring, chemicals in plastics, such as phthalates and BPA, have been identified in human population. Humans are exposed to the chemicals through the skin, nose, or mouth. Although the exposure level varies depending on geography and age, most individuals experience simultaneous exposure to lots of these chemicals. Average levels of everyday exposure are usually below the levels estimated not to be safe, but more research needs to be carried out to determine the effects of exposure to low dose on humans [1]. A lot is not known on how severely

individuals are physically affected by the exposure to these chemicals. Some of the chemical additives used in the production of plastics can cause dermatitis on contact with human skin [2]. In various plastics, these toxic chemicals are used in trace quantities, but significant testing is frequently required to ensure the toxic elements are contained and kept within the plastic by an inert material or polymer [2].

Also, it can affect humans by creating an eyesore which interferes with the recreational activities and gratifying pleasure of the natural environment, especially in beaches and street waterways. Due to the plastic products pervasiveness, majority of the human population is frequently exposed to the chemical additives and components of plastics. Over 95% of adults in the US have had detectable levels of bisphenol A in their urine. The exposure to chemicals such as bisphenol A have been associated with disruptions in sexual maturation, fertility, reproduction, and other health effects. Also, some specific phthalates have caused similar biological effects.

The Marine Conservancy has projected the disintegration rates of many plastic products. It is expected that a foam plastic cup can take 50 years, a plastic beverage holder will take 400 years, a disposable nappy will take 450 years, and fishing line will take 600 years to degrade [3]. Waste generation such as plastic wastes have been a major global challenge [4]. Plastic pollution may affect public health. Due to the increasing use of some chemical additives in the production of plastic, plastics have damaging effects that are carcinogenic, toxic or cause endocrine disruption. Some of these chemical additives are used as brominated flame retardants and phthalate plasticizers [5]. Although bio-monitoring, additives in plastics, like phthalates and bisphenol A, have been seen in the human populace. Humanity is exposed to these chemical additives via mouth, nose, skin, or eye. A lot is not yet known on how harshly human race is tangibly affected by these chemical additives. Many of these additives used in the production of plastics cause dermatitis on contact with the skin of a human [2]. Due to the widespread use of plastic products, the human race is continuously pre-exposed to the chemical constituents of plastics.

About 95 percent of adults in the developed countries such as the US have had detectable bisphenol A amounts in their urine. Exposure to chemical additives such as phthalate and bisphenol A has been linked to disruptions in fertility, sexual maturation, reproduction, and other health-related effects [7]. Also, certain phthalates lead to similar biological effect. Bisphenol A affects the expression of the gene related to the thyroid hormone alignment, which has effect on biological roles like metabolic rate and development. Potentially, bisphenol A reduces thyroid hormone receptor activities by reducing TR transcriptional corepressor activities. It then declines the levels of thyroid hormone-binding proteins which bind to the tri-iodothyronine. In affecting the thyroid hormone axis, bisphenol A exposure leads to thyroid impairment, hypothyroidism [6]. Bisphenol A can disrupt usual physiological levels of sex-enhancing hormones. This is done by binding to globulins which typically bind to sex hormones; estrogens and androgens, resulting in the interruption of the equilibrium between the two sex hormones. Bisphenol A also affects the catabolism and the metabolism of these sex hormones. It acts as either an anti-androgen or estrogen, causing interruptions in the production of sperm and gonadal development [6].

In an effort to mitigate the problems of plastic pollution, many countries around the world have joined in banning the use of plastic packages, with more states expected to join the league. In 2017, Kenya and Tunisia joined the league of African countries that place a ban on the use of plastic packages. Other countries in Africa include Mali, Cameroon, Uganda, Tanzania, South Africa, etc. Although, most of these countries, like Uganda, are yet to fully implement and enforce the law banning the use of plastic bags. Sadly, Nigeria is yet to look towards this campaign for the plastics ban. In Asia, countries like China, Bangladesh, Cambodia, India, Indonesia, Malaysia, and Taiwan, have either banned or increased taxes on plastic packages. In Europe, the Netherlands, France, UK, Italy, Germany, etc. have either banned or placed taxation on the use of plastic containers. In North and South America, sadly, the United States is yet to put a ban on plastic bags into effect. Nevertheless, Mexico, some Canadian provinces, Argentina, Chile, Colombia have taken measures to reduce or discourage the use of synthetic (plastic) packaging materials. The need to place a ban on plastic bags cannot be overemphasized.

There are lots of unknown on the direct consequences of plastic pollution on the sustainability of the seafood value chain, and the associated public health concerns of consuming plastic contaminated seafood, even as the use and acceptability of plastic materials and the resultant waste accumulations and environmental degradations have shown a mean increase recently, in spite of the numerous political and apolitical movements and mobilizations countering the random use and acceptability of plastic packaging materials and related ecological contamination and pollution [142]. There is a necessity for thorough research to be carried out to ascertain–through scientific, logical, and empirical approaches–the effects plastic pollution have on the global food value chain, food safety and security, and public health.

With the increasing global plastic pollution, aquatic animals, seafood, in particular, may be endangered. Also, the health of seafood consumers around the world may be at risk. Due to the increasing use of some chemical additives in plastic production, plastics have detrimental impacts that are carcinogenic, toxic, and stimulate endocrine disruption. Some of the chemical additives used–phthalate plasticizers, bisphenol A, brominated flame retardants, etc.–have been associated with various health challenges. In June 2018, a pilot whale was seen barely alive and later died, in a canal at Southern Thailand near the border with Malaysia after swallowing over 80 pieces of plastic bags weighing up to 3Ib. Experts suggested the plastic bags may have prevented the whales from eating. Thorough research is required to determine the impacts plastic pollution may have on the

seafood value chain and to ascertain its resultant effects on the health of consumers.

The research focused on the impacts of plastic pollution on human health, as well as the health implications of consuming plastic contaminated seafood. The study will aim at ascertaining and quantifying the potential effects of plastic pollutions and its associated chemical components–bisphenol A (BPA), phthalates, etc.–on lifespan of seafood and human health, with more focus on health consequences of consuming plastic contaminated seafood, such as tilapia, shrimp, crabs, etc. using rat model and, if possible, human model. The result of this study (research) will be valuable to policymakers and environmental agencies on designing the bench levels for monitoring purpose to checkmate the incidence of plastic pollution.

2. Plastic components and Their Effects

2.1. Microplastics

There are many ways through which plastics may interact with or impact wildlife. For microplastics (plastic particles less than 4.75 mm in diameter), ingestion is the key concern. Microplastics ingestion have been indicated to occur for various organisms.

2.1.1. Effect of Microplastics on Wildlife

This can occur through many mechanisms, ranging from the uptake by filter-feeders, to swallowing from the surrounding water, or the consumption of organisms which previously ingested microplastics [8]. There are many potential effects linked with microplastics at different biological levels, ranging from sub-cellular to the ecosystems, but many research focused on the effects in individual adult organisms.

Ingestion of microplastic rarely leads to mortality in organisms. As a result, the values of lethal concentration (LC) which are usually measured and reported for pollutants and contaminants do not exist. There are few exceptions: exposure of common goby to pyrene and polyethylene; Asian green mussels exposed to PVC (polyvinylchloride); and neonates of *Daphnia magna* exposed to polyethylene [8-10]. However, in such studies, exposure to and concentrations of microplastics far exceeded levels that would be encountered in natural environment (even in a highly contaminated environment). There is growing evidence that ingestion of microplastic can affect prey consumption, leading to depletion of energy, inhibited growth, and impacts fertility. When organisms swallow microplastics, it may take up space in their gut and gastrointestinal tract (GI), leading to reductions in feeding space and signal. The feeling of fullness reduces food intake, and usually lead to malnourishment and weakness. Evidence of impacts of reduced consumption of food include:

1. Reduced development and growth of langoustine [12].
2. Reduced survival and reproducibility in copepods [11], slower rate of metabolism and survival in Asian green mussels [9].
3. Reduced Daphnia growth and development [10].
4. Reduced energy stores in lugworms and shore crabs [13, 14].

Many organisms do not show changes in feeding after ingestion of microplastics. Many organisms, including suspension-feeders (such as European flat oysters, oyster larvae, Pacific oysters, urchin larvae) and detritivorous (e.g., amphipods, isopods) invertebrates show no microplastics impact [15]. Generally, however, it's possible that for several organisms, the presence of particles of microplastics in the gut (where food ought to be) may have some negative biological impacts.

2.1.2. Effect of Microplastics on Humans

Consumption of seafood represents one major pathway for the exposure of human to microplastic. Currently, there is little evidence of the impact of human exposure to microplastics. Despite having unclear evidence of health impacts, there is ongoing research on the risk of potential exposure, including its effects on human and aquatic animals [142]. The smallest particles — micro–and nano-particles are of greatest concern to human health. Particles must be very small enough to be consumed. There are many ways of ingesting plastic particles: consuming aquatic products which contain microplastics, orally through water, inhalation of air particles, or through skin via cosmetics (identified as possible, but very unlikely) [16]. Microplastics may pass up to higher levels in food chain. This can take place when species consume organisms of lower levels in the food chain, which contain microplastics in the tissue or gut [17]. Microplastics presence at higher levels of food chain in fish has been reported and documented [18, 19].

One factor which likely limits the dietary uptake by humans is that microplastics in fish have a tendency to be present in the digestive tract and gut — which are fish parts not typically consumed [17]. The microplastics presence in fish beyond the gastrointestinal tract (GI), e.g. in tissue, is yet to be studied in detail [20]. Micro–and nano-plastics in bivalves (oysters and mussels) cultured for human intake have been identified also. However, human exposure and potential risk to human is yet to be identified or quantified [21].

Also, plastic fibres have been detected in other foods, such as honey, table salt, and beer [22-24]. However, the authors suggested insignificant health risks due to this exposure.

Currently, levels of the ingestion of microplastics are unknown. Little is known about how such plastic particles interact in the body. It can be the instance that microplastics simply pass through the gastrointestinal tract (GI) without interaction or impact [25]. For example, a study of North Sea fish reported that 80% of fish with detected microplastics had only one particle — the outcome suggests that after ingestion, plastic does not persist for a long period of time [26]. In contrast, concentrations in mussels can be significantly higher.

Three likely toxic effects of plastic particles have been put forward: the release of persistent organic pollutants (POPs) adsorbed to the plastics, leaching of plastic additives, and plastic particles themselves [27]. No evidence of harmful effects exists to date. However, the precautionary principle indicate that this is not suggestion against taking exposure seriously. As microplastics are hydrophobic (insoluble in water), and have a high ratio of surface area-to-volume, they can sorb environmental contaminants (for example, polychlorinated biphenyl; PCB). If there is significant accumulation of environmental contaminants, then there is the likelihood that these concentrations may 'biomagnify' up food chain to higher levels. PCBs biomagnification varies by environmental conditions and organisms; multiple studies showed no evidence of uptake of PCBs by organisms despite ingestion [28] while some mussels, for instance, have shown the ability to transfer certain compounds into their digestive glands [29]. Currently, there is little or no reliable evidence of persistent organic pollutants (POPs) accumulation or leached plastic additives in humans. Continuous research in this area is required to better understand the role of plastics in broader ecosystems and the associated risk to human health.

2.2. Bisphenol A

Bisphenol A (BPA) can disrupt normal, regular physiological levels of sex hormones. BPA does this by binding to globulins which normally bind to the sex hormones such as estrogens and androgens, resulting to disruption in the balance between the two sex hormones. Also, bisphenol A can affect the catabolism or the metabolism of sex hormones. It always acts as an anti-estrogen or anti-androgen, which can lead to disruptions in sperm production and gonadal development. BPA affects gene expression connected to the thyroid hormone axis that affects biological functions like development and metabolism. Bisphenol A can reduce the thyroid hormone receptor (TR) activities by raising TR transcriptional co-repressor activities. This then reduces the levels of thyroid hormone binding protein which bind to triiodothyronine. Through affecting the thyroid hormone axis, exposure to bisphenol A can lead to hypothyroidism.

Bisphenol A (BPA) is organic synthetic compound with chemical formula $(CH_3)_2C(C_6H_4OH)_2$, which belongs to the group of bisphenols and diphenylmethane derivatives, with two groups of hydroxyphenyl. It is a solid which is colorless and soluble in organic solvents. BPA is poorly soluble in water; 0.344 wt percent at 83 °C [30]. Bisphenol A is a xenoestrogen, showing estrogen-mimicking, hormone-like properties [32], raising concern about its suitability in food containers and some consumer based products. The food additives such as sugar alcohols [34, 35] added to foods directly during processing, and the undesirable substances such as methanol and ethyl carbamate [36, 37] in some food products are already enough. Ever since 2008, many governments have investigated its safety and placed restrictions on its usage, which impelled several retailers to withdraw polycarbonate products. The Food and Drug Administration (FDA) has ended its BPA authorization of the use in infant formula packaging and baby bottles, due to market abandonment, not safety [33]. The EU and Canada have banned bisphenol A use in baby bottles. Type 3 (PVC) can contain BPA as an antioxidant in "flexible PVC" make softer by plasticizers [30], but not rigid PVC such as siding, pipe, and windows.

2.2.1. Health Effects of Bisphenol A

BPA has been reported to bind to both of nuclear estrogen receptors (ERs), ERβ and ERα [38]. Its potency is 1000–to 2000-fold less than estradiol [38]. BPA can both mimic estrogen action and antagonize estrogen, showing that it is a partial agonist of the ER or selective estrogen receptor modulator (SERM) [38]. At high concentrations, bisphenol A also binds to androgen receptor (AR) and acts as an antagonist of the AR [38]. In addition to binding to receptor, it has shown to affect Leydig cellsteroidogenesis, including affecting aromatase expression and 17α-hydroxylase/17,20 lyase and interfering with the binding of LH receptor-ligand [38].

In 1997, the adverse effects of low-dose exposure to bisphenol A in laboratory animal models were first proposed [39]. Modern studies began finding likely associations with health issues caused by BPA exposure during development and during pregnancy.

A study in 2007 investigated the interaction between estrogen-related receptor γ (ERR-γ) and BPA's. This orphan receptor (unknown endogenous ligand) behaves as a transcription constitutive activator. Bisphenol A seems to bind strongly to estrogen-related receptor γ (dissociation constant = 5.5 nM), but weakly bind to the ER [40]. Bisphenol A binding to estrogen-related receptor γ preserves its basal constitutive activity [40]. It can protect it from deactivation from selective estrogen receptor modulator (SERM) afimoxifene (4-hydroxytamoxifen) [40]. This could be the mechanism by which bisphenol A acts as a xenoestrogen [40]. Different ERR-γ expressions in different body parts may account for variations in the effects of bisphenol A. BPA has also been shown to act as a GPER agonist; GPR30 [41].

According to the EFSA (European Food Safety Authority), bisphenol A constitutes no health risk to consumers of every age group (including adolescents, unborn children, and infants) at current levels of exposure [42]. But in 2017 the European Chemicals Agency (ECA) concluded that bisphenol A should be enlisted as substance of very high concern deu to its endocrine disruption properties. In 2012, the US FDA banned BPA use in baby bottles [43].

The Environmental Protection Agency also maintains that is no health concern of BPA exposure. In 2011, the chief scientist of the UK's Food Standards Agency, Andrew Wadge, commented on a 2011 study by the US on BPA dietary exposure of adult humans [44], saying, that this corroborates other independent research and studies, and adds to evidence that bisphenol A is quickly absorbed, eliminated, and detoxified from humans–therefore is not a health concern

[45].

In 2015, the Endocrine Society said that the results of ongoing laboratory studies gave grounds for concern on the potential health hazards of EDCs–including bisphenol A–in the environment. It went further to state that on the precautionary principle basis, these substances have to be assessed continuously and tightly regulated [46]. A 2016 literature review stated that the potential harms posed by bisphenol A were topic of scientific debates and that further research was a priority due to the connection between exposure to BPA and adverse health effects on human including developmental and reproductive effects and metabolic disease [47].

2.2.2. Bisphenol A Substitutes

The concerns about bisphenol A health effects have led many manufacturers to replace bisphenol A with substitutes such as diphenyl sulfone and bisphenol S (BPS). However, health concerns are raised about the use of these substitutes.

2.2.3. Environmental Effects of Bisphenol A

A 2005 study conducted in the US found that 91 to 98 percent of bisphenol A can be removed from water in the course of treatment at municipal water treatment plants [48]. However, a 2009 BPA meta-analysis in the surface water system indicated that BPA is present in surface water and also sediment in the United States and Europe [49]. In 2011, Environment Canada stated that BPA can presently be detected in municipal wastewater; initial assessment indicates that bisphenol A at low levels can harm organisms, including fish, over time.

BPA affects development, growth, and reproduction in aquatic organisms. Amongst freshwater organisms, fish species seem to be the most sensitive to BPA exposure. Evidence of endocrine-related effects in amphibians, reptiles, fish, and aquatic invertebrates has been reported at environmentally significant levels of exposure lower than those required to cause acute toxicity. There is an extensive variation in the values reported for endocrine-related effects, however many of the values fall within the range of 1μg/L–1 mg/L.

In 2009, the Royal Society published a review of the biological impact of plasticizers on wildlife with a focus on terrestrial and aquatic annelids, insects, fish, amphibians, molluscs, and crustaceans concluded that bisphenol A impairs development in amphibians and crustaceans, induces genetic aberrations, and affects reproduction in all laboratory animal groups [50]. BPA exhibits a very low acute toxicity as shown by its LD50 of 4 g/kg in mouse.

2.3. Bisphenol S

Bisphenol S (BPS) is used as a corrosion inhibitor and in the curing of fast-drying epoxy glues. It is also often used as a reactant during polymer reactions. Bisphenol S has increasingly become common as a building block in some epoxies and polycarbonates, after the public awareness that bisphenol A has estrogen-mimicking properties, and the popular belief that enough of BPA residues in the products to be unsafe. However, bisphenol S may have similar estrogenic effects to bisphenol A [51]. Bisphenol S is now used in a variety of common consumer goods and products [52, 53]. In some cases, bisphenol S is used where the legal restriction on BPA use allows products (especially plastic containers) containing bisphenol S to be labelled "BPA free" [54]. Also, BPS has the advantage of more stablility to light and heat than BPA [55]. To comply with the regulations and restrictions on BPA as a consequence of its well-known toxicity, manufacturers are gradually replacing it with other related compounds, mostly bisphenol S, as substitutes for industrial applications [56].

Also, BPS is used as anticorrosive agent in epoxy glues. BPS is chemically used as a reagent in reactions involving polymers. BPS has also been shown to occur in canned foods, such as tin cans [57]. Recently, in a study analyzing BPS in varieties of paper products globally, BPS was detected in 100 percent of airplane luggage tags, tickets, mailing envelopes, and airplane boarding passes [58]. In the study, very high BPS concentrations were found in samples of thermal receipt collected from cities in the US, Vietnam, Japan, and Korea. The concentrations of BPS were large and high but varied significantly, from tens of nanograms per gram (ng/g) to several milligrams per gram (mg/g) [58]. However, BPS concentrations used in thermal paper manufacturing are often lower compared to BPA concentrations [58]. Finally, BPS may get into the body of human by dermal absorption from the handling of banknotes [52].

Bisphenol S (BPS), an organic compound with chemical formula $(HOC_6H_4)_2SO_2$, has two phenol functional groups on the either side of a sulfonyl group. BPS is commonly used in the curing of fast-drying epoxy resin adhesives. BPS is a bisphenol, and a similar analog of BPA in which the $C(CH_3)_2$ (dimethylmethylene group) is replaced with a SO_2 (sulfone group).

Recent studies suggest that BPS also has endocrine disrupting properties, just like BPA [59, 60]. The presence of a hydroxy group on the benzene ring makes bisphenol S and bisphenol A endocrine disruptors. This phenol moiety allows BPS and BPA to mimic estradiol. In a research involving human urine, bisphenol S was found in 81 percent of the tested samples. This percentage can be likened to the bisphenol A which was found in 95 percent of urine samples [61]. Another study carried out on thermal receipt paper indicates that 88 percent of human exposure to bisphenol S is through receipts.

Thermal paper recycling can introduce bisphenol S into the paper production cycle and cause contamination of other types and kinds of paper products with bisphenol S. Recently, a study indicated presence of BPS in at least 70 percent of samples of household waste paper, potentially showing spreading of contamination of BPS through the recycling of paper. BPS is more resistant to (and unaffected by) environmental degradation than bisphenol A, and although not persistent cannot be considered as readily biodegradable [62].

2.4. Phthalates

Phthalates, also called phthalate esters, are the esters of phthalic acid. Phthalates are mostly used as plasticizers. Plasticizers are substances added to plastics during production to increase their flexibility, longevity, transparency, and durability. There primarily use is to soften polyvinyl chloride (PVC). Almost all the phthalates of lower-molecular-weight, those derived from C3-C6 alcohols, are gradually replaced in many plastic and non-plastic products in the US, Canada, and the EU over health concerns [63]. They are replaced by the phthalates of high-molecular-weight (those with more than C6 in their backbone, giving them increased durability and permanency). High-phthalate plasticizers dominated the markets in 2010; however, due to growing environmental awareness and perceptions as well as legal provisions, producers are increasingly compelled to use non-phthalate plasticizers. The ubiquity of plasticized plastics makes majority of individuals exposed to some phthalates levels. For instance, most people in the US tested by the US Centers for Disease Control and Prevention had multiple phthalates metabolites in their urine [64]. In many studies of rodents exposed to some phthalates, high doses have been showed to cause birth defects and change hormone levels.

Phthalates are used in a large product varieties, from enteric coatings of nutritional supplements and pharmaceutical pills to gelling agents, film formers, viscosity control agents, stabilizers, dispersants, suspending agents, lubricants, binders, and emulsifying agents. End-applications include glues and adhesives, agricultural adjuvants, building materials, textiles, personal-care products, detergents and surfactants, medical devices, packaging, children's toys, printing inks and coatings, pharmaceuticals, modelling clay, waxes, paints, and food products. Phthalates are also often used in caulk, paint pigments, sex toys made of alleged "jelly rubber", and soft plastic fishing lures. Phthalates are often used in a range of household applications such as floor tiles, food containers and wrappers, cleaning materials, shower curtains, vinyl upholstery, and adhesives. Personal-care items containing phthalates are perfume, eye shadow, moisturizer, hair spray, nail polish, and liquid soap [65]. Phthalates are also found in medical applications (such as devices used for blood transfusion and catheters) and modern electronics. The most widely used phthalates are diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and di (2-ethylhexyl) phthalate (DEHP). Due to its low cost, DEHP was the predominant plasticizer used worldwide in PVC [66]. Benzylbutylphthalate (BBP) is used in the production of foamed polyvinyl chloride, which is used mainly as a flooring material, though its use is rapidly decreasing in the Western nations. Phthalates with small R' and R groups are used as solvents in pesticides and perfumes.

Table 1. *Table of the most common phthalates.*

Name	Abbreviation	Structural formula	Molecular weight (g/mol)	CAS No.
Dimethyl phthalate	DMP	$C_6H_4(COOCH_3)_2$	194.18	131-11-3
Diethyl phthalate	DEP	$C_6H_4(COOC_2H_5)_2$	222.24	84-66-2
Diallyl phthalate	DAP	$C_6H_4(COOCH_2CH{=}CH_2)_2$	246.26	131-17-9
Di-n-propyl phthalate	DPP	$C_6H_4[COO(CH_2)_2CH_3]_2$	250.29	131-16-8
Di-n-butyl phthalate	DBP	$C_6H_4[COO(CH_2)_3CH_3]_2$	278.34	84-74-2
Diisobutyl phthalate	DIBP	$C_6H_4[COOCH_2CH(CH_3)_2]_2$	278.34	84-69-5
Butyl cyclohexyl phthalate	BCP	$CH_3(CH_2)_3OOCC_6H_4COOC_6H_{11}$	304.38	84-64-0
Di-n-pentyl phthalate	DNPP	$C_6H_4[COO(CH_2)_4CH_3]_2$	306.40	131-18-0
Dicyclohexyl phthalate	DCP	$C_6H_4[COOC_6H_{11}]_2$	330.42	84-61-7
Butyl benzyl phthalate	BBP	$CH_3(CH_2)_3OOCC_6H_4COOCH_2C_6H_5$	312.36	85-68-7
Di-n-hexyl phthalate	DNHP	$C_6H_4[COO(CH_2)_5CH_3]_2$	334.45	84-75-3
Diisohexyl phthalate	DIHxP	$C_6H_4[COO(CH_2)_3CH(CH_3)_2]_2$	334.45	146-50-9
Diisoheptyl phthalate	DIHpP	$C_6H_4[COO(CH_2)_4CH(CH_3)_2]_2$	362.50	41451-28-9
Butyl decyl phthalate	BDP	$CH_3(CH_2)_3OOCC_6H_4COO(CH_2)_9CH_3$	362.50	89-19-0
Di(2-ethylhexyl) phthalate	DEHP, DOP	$C_6H_4[COOCH_2CH(C_2H_5)(CH_2)_3CH_3]_2$	390.56	117-81-7
Di(n-octyl) phthalate	DNOP	$C_6H_4[COO(CH_2)_7CH_3]_2$	390.56	117-84-0
Diisooctyl phthalate	DIOP	$C_6H_4[COO(CH_2)_5CH(CH_3)_2]_2$	390.56	27554-26-3
n-Octyl n-decyl phthalate	ODP	$CH_3(CH_2)_7OOCC_6H_4COO(CH_2)_9CH_3$	418.61	119-07-3
Diisononyl phthalate	DINP	$C_6H_4[COO(CH_2)_6CH(CH_3)_2]_2$	418.61	28553-12-0
Di(2-propylheptyl) phthalate	DPHP	$C_6H_4[COOCH_2CH(CH_2CH_2CH_3)(CH_2)_4CH_3]_2$	446.66	53306-54-0
Diisodecyl phthalate	DIDP	$C_6H_4[COO(CH_2)_7CH(CH_3)_2]_2$	446.66	26761-40-0
Diundecyl phthalate	DUP	$C_6H_4[COO(CH_2)_{10}CH_3]_2$	474.72	3648-20-2
Diisoundecyl phthalate	DIUP	$C_6H_4[COO(CH_2)_8CH(CH_3)_2]_2$	474.72	85507-79-5
Ditridecyl phthalate	DTDP	$C_6H_4[COO(CH_2)_{12}CH_3]_2$	530.82	119-06-2
Diisotridecyl phthalate	DITP	$C_6H_4[COO(CH_2)_{10}CH(CH_3)_2]_2$	530.82	68515-47-9

Approximately 8.4 million tons of plasticizers are manufactured globally per annum, of which Europeans produce approximately 1.5 million metric tons. Approximately 70 percent of which are phthalates, down from approximately 88 percent in 2005. The remaining 30 percent are alternative chemistries. Plasticizers contribute 10 to 60 percent of total weight of plasticized products. Recently in the US and Europe, regulatory developments have led to a change in the consumption of phthalates, with the higher phthalates (DIDP and DINP) replacing DEHP as general purpose choice of plasticizer because DINP and DIDP were not categorized as being hazardous. All these phthalates

mentioned are now restricted and strictly regulated in various products. DEHP, though most applications are shown to have no risk when studied with recognized risk assessment methods, has been characterized as a Category 1B reprotoxin, and is currently on the Annex XIV of the EU's REACH legislation. DEHP was phased out in the Europe under the EU's REACH and can be used only in specific circumstances if an authorization is granted. Authorizations are only granted by the European Commission (EC), after obtaining opinion of the Risk Assessment Committee (RAC) and the Socio-economic Analysis Committee (SEAC) of the European Chemical Agency (ECHA).

2.4.1. Properties of Phthalate

Phthalate esters (Phthalates) are the esters of dialkyl or alkyl aryl of phthalic acid (also known as 1,2-benzenedicarboxylic acid). When phthalates are added to plastics, they allow the long molecules of polyvinyl to slide against one another. Phthalates have clear consistency of syrupy liquid and show high oil solubility, low volatility, and low water solubility. The polar carboxyl group contributes a little to the phthalates physical properties, with the exception of when R' and R are very small (such as methyl or ethyl groups). Phthalates are odorless, colorless liquids produced by the reaction of phthalic anhydride and an appropriate alcohol (often 6–to 13-carbon).

2.4.2. Environmental Impacts of Phthalates

Phthalates are released into the environment easily. Overall, they do not persist in the environment due to rapid biodegradation, anaerobic degradation, and photo degradation. Outdoor air concentrations of phthalates are higher in suburban and urban areas than in remote and rural areas [67]. Also, they pose no acute toxicity. Due to their volatility, DMP and DEP are detected in the air in higher concentrations in comparison with the less volatile and heavier DEHP. Higher air temperatures lead to higher phthalates concentrations in the air. Polyvinyl chloride flooring leads to higher BBP and DEHP concentrations, which are more predominant in dust [67]. A 2012 study of children in Sweden found that phthalates from PVC flooring penetrate into their bodies, indicating that children do not only ingest phthalates from food but also through the skin and by breathing [68].

The major source of DEHP and other types of phthalates in the general population is believed to be diet. Fatty foods such as meats, milk, and butter are major sources too. Studies show that phthalates exposure is higher from the ingestion of some foods, rather than exposure through water bottles as is most frequently first thought of with plastic products and plastic chemicals [69]. Low-molecular-weight phthalates such as BBzP, DBP, and DEP may be dermally absorbed. Also, exposure through inhalation is significant with the very volatile phthalates [70]. Another study, done between 2003 and 2010 analyzing data from 9,000 people, found that individuals who reported that they have eaten at fast food restaurant had very higher levels of two distinct phthalates (DiNP and DEHP) in samples from their urine. Even small fast food consumption caused higher presence of phthalates in their body. Individuals who reported consuming only a little fast food had levels of DEHP that were 15.5% higher and levels of DiNP that were 25% higher than those who reported they had consumed none. For people who reported consuming a substantial amount, the increase was 24% and 39%, respectively [71].

A 2008 Bulgarian study reported that higher DEHP dust concentrations were detected in homes of children with allergies and asthma, compared with homes of healthy children [72]. The author of the study said that the DEHP concentration was shown to be significantly connected with wheezing in the last one year as reported by the parents [72]. Phthalates were detected in almost all the sampled home in Bulgaria. Same study found that DnOP, DEHP, and BBzP concentrations were significantly higher in dust samples taken from homes where polishing agents were made use of. Data was collected on flooring materials, but there was no significant difference in the concentrations between homes where no polish was made use of that have balatum (linoleum or PVC) flooring and the homes with wood. High dusting frequency did decrease the concentration [72].

Generally, exposure of children to phthalates is more than that of adults' exposure. A 1990s Canadian study which modeled ambient exposures estimated that DEHP daily exposure was 19 μg/kg bodyweight per day in toddlers, 6 μg/kg bodyweight per day in adults, 14 μg/kg bodyweight per day in children, and 9 μg/kg bodyweight per day in infants [70]. Infants and toddlers are at utmost risk of exposure, due to their mouthing behavior characteristics. Body care product containing phthalates is another source of infant exposure. The authors of a study in 2008 observed that reported use of infant shampoo, infant lotion, and infant powder were connected with increased concentrations of phthalate metabolites in infant urine, and the association is lesser in older infants and strongest in younger infants. Their findings suggest that exposures through skin may significantly contribute to body burden of phthalates in this young population. Although they did not examine the health outcomes, however, they noted that younger infants are most vulnerable and susceptible to the phthalates potential adverse effects due to their metabolic capabilities, increased dosage per unit surface area of their body, and developing reproductive and endocrine systems [73].

Infants and hospitalized children are mainly susceptible to phthalate exposures. Medical devices and tubing can contain 20 to 40 percent DEHP (Di (2-ethylhexyl) phthalate) by weight, which can leach out of tubing easily when exposed to heat; as with warm saline/blood [73]. Many medical devices contain phthalate esters including, but not limited to, respiratory tubing, IV tubing, gloves, and nasogastric tubes. The US FDA did an extensive phthalates risk assessment in the medical setting and reported that neonates can be exposed to over five times higher than the permitted daily tolerable intake. This finding led to the FDA conclusion that Children undergoing some medical procedures may be a representative of the population at increased risk of the effects of DEHP

[74].

The Danish Environmental Protection Agency in 2008 detected multiples of phthalate esters in erasers and warned of the health risks when children often chew and suck them. The European Commission Scientific Committee on Health & Environmental Risks (SCHER), nevertheless, considers that, even in the circumstance when children bite off some pieces from erasers and swallow them directly, it is not likely that this exposure level poses a health risk.

Phthalates can also be detected in medications, where they are often used as inactive ingredients in the production of enteric coatings. It is unknown how several medications are made with phthalates, but some include theophylline, omeprazole, didanosine, and mesalamine. It is very difficult for human to completely be free from phthalates exposure. Recently, a study reported that the monobutyl phthalate (the DBP metabolite) concentrations in the urine of Asacol (a particular mesalamine formulation) users was over 50 times higher than the mean of that of nonusers [75]. The study indicated that exposures from medications containing phthalates can exceed population levels from other known sources by far [75]. Medications containing DBP raise concern about the health risks due to high level of exposures connected with taking these medications, particularly in the population vulnerable segments, including children and pregnant women [75].

In 2008, the US National Research Council recommended for investigations on phthalates cumulative effects as well as the cumulative effects of other anti-androgens. It criticized the US EPA guidance, which stipulate that, when cumulative effects are examined, the chemicals examined should have similar structures or similar mechanisms of action, as very restrictive. Instead, it made a recommendation that the effects of chemicals which cause similar adverse outcomes (health effects) should be examined cumulatively [76]. Consequently, the effect of phthalates would be examined alongside other antiandrogens, which otherwise may be excluded because their structures or mechanisms are different.

2.4.3. Health Risks and Physiological Effects of Phthalates

a) Endocrine disruption

An endocrine disruptor is any substance or compound that interferes with normal mechanisms of hormonal system that allow the interactions of a biological organism with its environment. In scientific community, phthalates are generally classified as endocrine disruptors [77-79]. Many scientific studies show the possibility that phthalates are endocrine disruptors in humans. Endocrine disruptors show many behaviors that could make their study a challenge. There can be a gap between when somebody is exposed to endocrine disruptor and symptoms manifesting themselves; fetal and early childhood exposure, in particular, may have implications later in adulthood [73, 80]. Many studies characterize this period of postnatal and fetal development as particularly significant to development, but it is difficult studying this; it is apparently a huge challenge to measure the exposure to an endocrine disruptor during fetal development, and decades later diagnosing any associated health problems. In addition, endocrine disruptor exposures can be transmitted epigenetically to one's offspring without their direct exposure to the endocrine disruptors [81]. Particularly, low exposure levels may still have significant effects. Also, exposure to several endocrine disruptors across a range of compounds (not just phthalates alone) may combine synergistically to cause a greater effect [73, 80]. Evaluating the actual effects of a particular compound such as a specific phthalate requires examining the cumulative exposure across several compounds, rather than isolating one compound for evaluation [80].

A common concern about exposure to phthalate is the likelihood that it is the main cause of a drop in the male fertility [82; 83; 84]. Studies have indicated that phthalates cause abnormalities in reproductive systems of animals [85], with the highest effects occurring when the animal is exposed during the period of gestation and immediately thereafter [86]. Several studies on adult male humans indicate the related result that exposure to phthalate correlates with the worsening metrics of male fertility, for example the amount of damaged DNA in sperm, semen quality, decreased semen volume, decreased sperm motility, and other metrics [86, 87]. Phthalates causing damage to male reproductive system is possible [88], and continues to be studied and researched.

Early research also indicates phthalate exposure may be connected with diabetes and insulin resistance, obesity, breast cancer [89], immune function, endocrine disruption, and metabolic disorders. There are possible (though inconclusive) associations between adverse child neurodevelopment and phthalate exposure, including ADHD development and autistic behaviors as well as lower cognitive and motor development [90, 91]. In countless cases, there are studies that indicate the association between these negative outcomes and phthalates, as well as studies which show no connection. In all cases, comprehensive studies are required to demonstrate uncontestably what effect exposure to phthalates has on the health of human. A recent review paper of the Nature Reviews Endocrinology gives some advice for avoiding phthalates exposure for concerned individuals; while they stated no evidence shows this advice will affect one's health positively, they suggest (1) eliminating packaged or canned food in order to limit the ingestion of DEHP phthalates that leached from plastics (2) eliminating the use of any personal care product such as perfume, cosmetics, moisturizer that contain phthalates, and (3) eating balanced diet to avoid intake of many endocrine disruptors from only one source. Eliminating personal products which contain phthalates may be particularly difficult or unlikely due to some nations such as the US not requiring them to be make known in a list of ingredients [92].

b) Endocannabinoid system disruption

Phthalates have been shown to block CB_1 as allosteric antagonists [93].

c) Other physiological effects of phthalates

There could be a link between endocrine disruption and

obesity epidemic and metabolic interference. Studies done on mice exposed to phthalate esters in utero did not lead to metabolic disorder in adults [94]. On the other hand, in a national cross-section of American men, concentrations of many prevalent metabolites of phthalates showed statistically significant correlations and association with insulin resistance and abnormal obesity [94]. A metabolite of DEHP, called Mono-ethylhexyl-phthalate (MEHP), has been detected to interact with all three peroxisome proliferator-activated receptors (PPARs) [94]. PPARs are members of nuclear receptor super family. Author of the study stated that the roles of peroxisome proliferator-activated receptors in the metabolism of carbohydrate and lipid raise questions on their activation by a subclass of the pollutants, tentatively called metabolic disrupters. Phthalates (phthalate esters) belong to this metabolic disruptors' class. It is likely that, over several years of the exposure to these metabolic disruptors, they can be able to deregulate complex pathways for metabolism in a subtle manner [94].

Large amounts of some specific phthalates fed to rodents shown to cause harm to their liver and testes. Also, initial rodent studies indicated hepatocarcinogenicity. After this result, di(2-ethylhexyl) phthalate was enlisted as a likely carcinogen by IARC, WHO, and EC. Advanced studies on primates later showed that the mechanism is specific to the rodents; human is resistant to the effect. The classification of di(2-ethylhexyl) phthalate as a likely carcinogen was later withdrawn.

2.4.4. Identification of Phthalates in Plastics

Phthalates are used in several, but not all, formulations of PVC, and there are no specific requirements for labeling of phthalates. Plastics made of PVC are typically used for many bags, medical tubing, containers and hard packaging, and are labelled "Type 3" for recycling purposes. However, phthalates presence instead of other plasticizers is not written on PVC items. Only uPVC (unplasticized PVC), which is mostly used as a hard material for construction, has no plasticizers. If a further accurate test is required, chemical analysis can establish phthalates presence; for example by liquid chromatography or gas chromatography.

Polyethylene terephthalate (PET, Terylene, PETE, Dacron) is the main chemical substance used to package many sodas and bottled water. Products that contain PETE are labeled "Type 1" for recycling purposes; with a "1" in the recycle triangle. Though the word "phthalate" is in the name, PETE does not make use of phthalates as plasticizers and for plasticizing. The phthalate ester plasticizers and the terephthalate polymer PETE are different substances chemically. Despite this, however, many studies have detected phthalates such as DEHP in soda and bottled [95]. One of the hypotheses is that these may be introduced during plastics recycling [95].

2.5. Tetrabromobisphenol A (TBBPA)

The reaction of bromine with bisphenol A produces tetrabromobisphenol A (TBBPA). Most commercial tetrabromobisphenol A products consist of a mixture which differ in the degree and rate of bromination with this formula; $C_{15}H_{16-x}Br_xO_2$ where x = 1 to 4. The fire-retarding properties of TBBPA correlate with %Br. The yearly consumption in Europe was estimated as 6.200 tonnes in 2004. Tetrabromobisphenol A is mostly used as a reactive constituent of polymers, which means that it is integrated into the backbone of the polymer. It is used for the preparation of fire-resistant polycarbonates by the replacement of some BPA. A lower grade of tetrabromobisphenol A is used in the preparation of epoxy resins used in the printed circuit boards.

In December 2011, a study report was published by the EFSA (European Food Safety Authority) on the exposure of tetrabromobisphenol A and its derivatives in food. The 2011 study, which examined 344 food samples from fish and other seafood, concluded that current dietary exposure to tetrabromobisphenol A in the EU does not raise any health concern. Also, EFSA determined that additional exposure to TBBPA, particularly of young children, from house dust is not likely to raise any health concern [96]. Many recent studies suggest that tetrabromobisphenol A may be an immunotoxicant and endocrine disruptor. As an endocrine disruptor, tetrabromobisphenol A may interfere with both androgens and estrogens [97]. Additionally, TBBPA structurally mimics thyroid hormone thyroxin (T_4) and may bind more strongly and firmly to the transport protein transthyretin than the thyroid hormone thyroxin (T_4) can do, likely interfering with normal activity of T_4. Also, TBBPA may likely suppress immune responses through the inhibition of CD25 receptors expression on T cells, inhibiting their activation, and through decreasing natural killer cell activity [98, 99]. The acute toxicity of tetrabromobisphenol A is reported as being very low in rodents with oral LD50 >10,000 mg/kg in mice and >50,000 mg/kg in rat. There is no available information on the acute toxicity in humans or other mammals after oral exposure.

A literature review on TBBPA in 2013 concludes that tetrabromobisphenol A does not produce adverse effects which might be associated with the disturbances in the endocrine system [100]. Furthermore, tetrabromobisphenol A is rapidly excreted in mammals and as a result does not have a tendency for bioaccumulation. Measured TBBPA concentrations in samples of human serum, house dust, and human diet are very low. TBBPA daily intakes in humans were estimated not to exceed a few ng/kg bodyweight per day. The general population exposures to TBBPA are also below the derived-no-effect-levels (DNELs) generated for endpoints of the potential concerns in REACH.

Tetrabromobisphenol A degrades to TBBPA dimethyl ether and to bisphenol A. An experiments in zebrafish (*Danio rerio*) made suggestion that during development, tetrabromobisphenol A may be toxic than either TBBPA dimethyl ether or BPA [101, 102].

2.6. Polybrominated Diphenyl Ethers (PBDEs)

Polybrominated diphenyl ethers, also known as PBDEs, are compounds of organobromine that are used as flame

retardant in a many products, including plastics, airplanes, motor vehicles, polyurethane foams, building materials, electronics, furnishings [103], and fabrics. Polybrominated diphenyl ethers are classified in relation to the average number of bromine atoms the molecule contains. The health hazards of the PBDEs have attracted increasing scrutiny. They have showed to decrease fertility in humans at the levels found in households [104]. Their chlorine analogs are the polychlorinated diphenyl ethers (PCDEs). Due to their persistence and toxicity, the industrial production of many PBDEs is restricted by the Stockholm Convention, a treaty aimed at controlling and phasing out major POPs (persistent organic pollutants).

Two main classes of PBDEs are the higher brominated PBDEs and the lower brominated PBDEs.

Lower brominated PBDEs

The lower brominated PBDEs average 1 to 4 atoms of bromine per molecule and are considered to be more dangerous as they bioaccumulate more efficiently. Lower-brominated polychlorinated diphenyl ethers are known to affect hormone levels in thyroid gland. Many studies have linked them directly to neurological and reproductive risks at some concentrations or higher [105].

Higher brominated PBDEs

The higher brominated PBDEs have average 5 or more atoms of bromine per molecule.

The commercial mixture, called pentabromodiphenyl ether, predominantly contains the pentabromo derivative (50 to 62%); but, the mixture also contains hexabromides (4 to 8%), and tetrabromides (24 to 38%), as well as traces amounts of the tribromides (0 to 1%). Similarly, commercial octabromodiphenyl ether is a homologs mixture: deca-, nona-, octa-, hepta-, and hexabromides

Since the 1990s, environmental concerns are raised due to the PBDEs high hydrophobicity and high resistance to the processes of degradation. While biodegradation is not regarded the main PBDEs pathway, the pyrolysis and photolysis can be of interest in the studies of the transformation of PBDEs [106, 107]. Individuals are exposed to low polybrominated diphenyl ethers levels through the ingestion of food and also through inhalation. Polybrominated diphenyl ethers bioaccumulate in blood, fat tissues, and breast milk. Personnel connected with the manufacture of products containing PBDE are exposed to the highest levels of polybrominated diphenyl ethers. In such instances, bioaccumulation is of particular concern, especially for personnel in repair and recycling plants working on products containing PBDEs [106]. Also, individuals are exposed to PBDEs in their domestic environment due to their prevalence in common domestic items. Studies in Canada detected significant PBDEs concentrations in common foods such as cheese, salmon, ground beef, and butter. PBDEs have also been detected at high levels in indoor dust, effluents from wastewater treatment plants, and sewage sludge. Increasing levels of PBDE were detected in the blood of aquatic mammals, like harbor seals [106].

There is increasing concern that polybrominated diphenyl ethers share the bioaccumulation and environmental long life properties of polychlorinated dibenzodioxins. Although, it is still unknown if PBDEs can be carcinogenic to individuals, although liver tumors developed in mice and rats that consumed extremely large quantities of decaBDE all through their lifetime. Currently, lower-brominated polybrominated diphenyl ethers are yet to be tested for cancer in animal models. IARC (International Agency for Research on Cancer) classified polybrominated diphenyl ethers as a Group 3 carcinogen (unclassifiable as to its human carcinogenicity) based on insufficient evidence of carcinogenicity in human and insufficient or limited evidence in experimental animal models. The EPA ascribes the cancer category Group D (unclassifiable as to its human carcinogenicity). However, the EPA assigns a suggestive evidence classification of carcinogenic potential for decaBDE. American Conference of Governmental Industrial Hygienists has no data regarding carcinogenic classifications for PBDEs [108].

PBDEs have been showed to have disrupting effects on hormone levels, particularly, on estrogen and thyroid hormones [109]. An animal study in 2009 conducted by the United States Environmental Protection Agency (EPA) showed that deiodination, glucuronidation, active transport, and sulfation may be involved in the disruption of thyroid homeostasis following perinatal exposure to polybrominated diphenyl ethers during time points of critical developmental *in utero* and soon after birth [110]. The adverse effects on the hepatic mechanism of the thyroid hormone disruption during human development have been indicated to persist into the adulthood. The EPA stated that polybrominated diphenyl ethers are mainly toxic to the developing brains in animals [110]. Peer-reviewed studies have indicated that a single dose given to mice during brain development can result to permanent behavioral changes, including hyperactivity [111].

Scientists from Sweden first reported that substances related to pentaBDE were bio accumulating in human breast milk [112]. The Swedish Society for Nature Conservation (SSNC) for the first time reported very high levels of the more highly brominated polybrominated diphenyl ethers (BDE-209) in peregrine falcons eggs [113]. Two forms of polybrominated diphenyl ethers, penta–and octaBDE, are not manufactured anymore in the US due to health and safety concern. Based on the comprehensive risk assessment in the Existing Substances Regulation 793/93/EEC, the EU has banned the use of octa–and pentaBDE completely since 2004. However, both are still detected in foam and furniture items made before the banning and phase-out was completed. The most common polybrominated diphenyl ethers used in electronics are decabromodiphenyl ether (decaBDE). DecaBDE is banned in the Europe for this use as well as in some states in the US. For polybrominated diphenyl ethers, EPA set reference dose of 7 μg/kg of body weight, which is understood to have no appreciable effects.

Increasing levels of polybrominated diphenyl ethers in the environment may be the cause of the growing incidence of feline hyperthyroidism [114]. A study in 2007 detected PBDE

levels in cats to be 20–to 100-fold greater than the median levels in adults in US, although it was inadequately powered to establish a connection between serum PBDE levels and hyperthyroid cats [115]. Subsequent studies have indeed showed such connection [116-118].

An experiment in 2005 conducted at the Woods Hole Oceanographic Institution showed that an isotopic signature of methoxy-PBDEs detected in whale blubber had carbon-14, a naturally occurring radioactive carbon isotope. Methoxy-PBDEs are made by some marine species [119]. If methoxy-PBDEs in the whale had come from man-made (artificial) sources, they would have had stable isotopes of carbon alone, as all PBDEs that are made artificially use petroleum as the carbon source; all carbon-14 (C14) would have long completely decayed from that source [120]. The isotopic signatures of the polybrominated diphenyl ethers themselves were not assessed. The carbon-14 may rather be in methoxy groups and enzymatically added to artificial polybrominated diphenyl ethers.

A study in 2010 found that children who had higher concentrations of PBDE congeners 47, 99 and 100 within the blood of their umbilical cord at birth recorded lower on tests of physical and mental development between the age bracket of one and six. The developmental effects were mostly evident at the age of four years, when full IQ and verbal scores were decreased 5.5 to 8.0 points for the ones with highest prenatal exposure after the correction for tobacco smoke exposure, sex, ethnicity, and mother's IQ [121, 122].

The State of California in August 2003 outlawed the sale of octa–and pentaBDE and products containing both, effective January the 1st, 2008. Polybrominated diphenyl ethers are ubiquitous in environment, and, according to the US EPA, exposure may pose health risks. The US EPA's Integrated Risk Information System stated that evidence shows that polybrominated diphenyl ethers may pose hepatic toxicity, neurodevelopmental toxicity, and thyroid toxicity [123]. In June 2008, the EPA set a safe daily level of exposure ranging from 0.1 to 7 ug/kg body weight each day for the four top common PBDE congeners [123]. The legislature of the United States' state of Washington in April 2007 passed a bill placing ban on PBDEs use. The legislature of the state of the Maine in May 2007 passed a bill banning the use of decaPBDE [123].

The EU made the decision to ban the usage of two types of flame retardants, in particular, polybrominated biphenyls (PBBs) and PBDEs in electronic and electric devices. This ban was formalized in the Restriction of Hazardous Substances (RoHS) Directive, and an upper 1 g/kg limit for the sum of PBDEs and PBBs was set [123]. The Institute for Reference Materials and Measurements in February 2009 released two certified reference materials to assist analytical laboratories in better detecting these two classes of flame retardants. These reference materials were customized to contain all relevant PBBs and PBDEs at levels close to the permitted limit. In May 2009, at an international level, the Parties in the Stockholm Convention for POPs (Persistent Organic Pollutants) decided to list commercial octaBDE and commercial pentaBDE as POPs. This listing is due to the heptaBDE and hexaBDE properties which are constituents of commercial octaBDE, and also to the properties of pentaBDE and tetraBDE, which are the major components of commercial pentaBDE [123].

3. Current Active Solutions to Plastic Pollution

3.1. Use of Biodegradable and Degradable Plastics

The biodegradable plastics usage has advantages and disadvantages. The biodegradables are biopolymers which degrade in industrial composters. The biodegradables do not degrade very efficiently in domestic and household composters, and during this slower process, emission of methane gas may occur. Also, there are other types of degradable materials which are not regarded to be biopolymers, as they are oil-based, related to other conventional plastics. These plastics can be made to be more degradable by the use of some additives, which help degrade them when exposed to Ultraviolet rays or other physical stressors. Nevertheless, biodegradation-promoting additives for polymeric materials have been shown not to significantly increase biodegradation [124]

Although degradable and biodegradable plastics have helped in reducing plastic pollution, there are a number of drawbacks. One concern about both types of plastics is they do not break down or degrade very efficiently in natural environments. In the natural environments, degradable plastics which are oil-based may break down to smaller fractions, and at this point they do not degrade any longer.

Some of the organisms that help degrade plastics are:

1) *Pestalotiopsis microspora*, endophytic fungus species able to degrade polyurethane.
2) *Galleria mellonella,* a caterpillar that digest polyethylene.
3) *Aspergillus tubingensis*, a fungus that digest polyurethane.

3.2. Policy

Some agencies like the US Environmental Protection Agency (EPA) and the United States Food and Drug Administration habitually do not evaluate the safety of new chemicals till after a negative side effect is reported. Once they realize a chemical may be toxic, they study to determine the reference dose for human, which is assessed to be the least observable adverse effect level. During the studies, a high dose is often tested to see if it can cause any adverse health effect, and if it does not, lower doses are taken to be safe as well. It does not consider the fact that with many chemicals, such as BPA, found in plastics; lower doses can have a noticeable effect [125]. Even with this complex evaluation process, some policies have been put in place so as to help alleviate plastic pollution and its associated effects. Government regulations that ban many chemicals from being

used in specific products of plastic have been implemented.

In Canada, the US, and the EU, bisphenol A has been banned from being used in the production of children's cups and baby bottles, due to the health concerns and the very higher vulnerability of younger children to BPA effects. Taxes have been put in place in order to discourage some specific ways of plastic waste management. The landfill tariff, for instance, creates an incentive to prefer to plastics recycling rather than putting them in landfills, by ensuring the latter is more expensive. Also, there has been standardization of the types of plastics which can be regarding as being compostable. The European Norm EN 13432 that was set by European Committee for Standardization (CEN), lists out the standards that plastics must meet, with respect to biodegradability and compostability, in order to receive official labeled as being compostable [126].

3.3. Incineration

Over 60 percent of used plastic medical equipment are incinerated instead of deposited in a landfill as precautionary measure to reduce disease transmission. This leads to significant decrease in the quantity of plastic waste that comes from the medical equipment. If plastic wastes are not incinerated and properly disposed of, harmful quantity of toxins could be released and dispersed as gases by air or as ash by waterways and air. Several studies have been conducted on the gaseous emissions which result from the process of incineration.

3.4. Collection

The two major forms of waste collection are the use of drop-off recycling centers and the curbside collection. About 87% of the population in the US (about 273 million individuals) have access to drop-off recycling centers and curbside. In curbside collection, available to about 63% of the US population (193 million people), individuals place designated plastics in special bin to be collected by a private or public hauling company. Many curbside programs collect two or more types of plastic resin; usually both HDPE and PETE inclusive. At drop-off recycling centers, available to 68% of the US population (213 million people), individuals take their recyclable items to a facility that is centrally located. Once collected, the plastic items are delivered to a handler or MRF (materials recovery facility) for sorting into streams of single-resin to increase the value of the product. The sorted plastics are baled to reduce the costs of shipping to reclaimers.

There are variable rates of recycling each type of plastic. In 2011, the overall rate of plastic recycling was approximately 8 percent in the US. Approximately 2.7 million tonnes of plastics were recycled in the United States in 2011. A number of plastics are often recycled more than others; in the same 2011, 29% of HDPE bottles and 29% of PET bottles as well as jars were recycled.

A new model for the collection of packaging from consumers for reusing it began in May 2019. It is named Loop. Consumers drop the package in some special shipping totes and a pickup will collect it. Partners include PepsiCo, Unilever, Procter & Gamble, Nestlé, Mars Petcare, The Clorox Company, Mondelēz, Danone, The Body Shop, Coca-Cola, and other firms [127].

The Loop service begun to function in May 21, 2019. It has begun with many thousand households, but there are just 60,000 households on the waitlist. The target is not stop single use plastic alone, but to generally stop single use. But even the durable plastics are not used in contact with foods [128].

3.5. Non-usage and Lessening Usage

The India Ministry of Drinking Water and Sanitation has requested many governmental departments to shun the use of plastic bottles when providing drinking water in governmental meetings, etc., and to rather make arrangements for providing drinking water without generating plastic waste. The Sikkim state has restricted the use of Styrofoam products and plastic water bottles during government meetings and functions. The state of Bihar has banned the use of plastic bottled water in governmental meetings and functions.

The 2015 National Games of India, organized in Thiruvananthapuram, was connected with green protocols. The Suchitwa Mission that aimed for zero-waste venues initiated it. To make the event free from disposables, there was ban on the use of disposable water bottles. Also, the event witnessed the use of reusable stainless steel tumblers and tableware. Athletes were served with steel flasks which are refillable. It is estimated that the green practices prevented the generation of 120 metric tons of disposable wastes.

In 2016 the city of Bangalore banned plastic for general purpose other than for a few special cases such as milk delivery, etc.

The Maharashtra state of India implemented the Maharashtra Plastic and Thermocol Products ban in 23 June 2018, and subjected plastic users to fines and also potential imprisonment for repeat offenders [129, 130]

Albania became the first nation in Europe to ban plastic bags of lightweight in July 2018 [131]. Blendi Klosi, Albania's environment minister, said that businesses producing, trading, or importing plastic bags <35 microns in thickness risk paying fines between €7900 and €11800 (1 million and 1.5 million lek).

In January 2019, the supermarket chain of the Iceland, which has specialization in frozen foods, vowed to drastically reduce or eliminate all plastic packaging by 2023 for its store-brand products [132].

A pair of two sisters, Isabel and Melati Wijsen, in Bali have pushed through efforts to the ban of plastic bags in 2019. Their Bye Bye Plastic Bags organization has spread to over 28 locations all over the world.

In 2019 the US state of New York banned the usage of single use plastic bags and at the same time introduced a fee of 5 cent for the use of single use paper bags. This ban placement will enter into full force in 2020. This will not

reduce the use of plastic bag in the New York state alone (23,000,000,000 per annum until now), but also stamp out or eliminate 12 million oil barrels used to produce plastic bags used by the New York state each year [133, 134].

In 2019, The Nigeria House of Representatives banned the import, usage, and production of plastic bags in the entire country [135].

In Israel, two cities, Herzliya and Eilat, made the decision to ban the use of cutlery and single use plastic bags on the beaches [136].

3.6. Creating Awareness

In order to create awareness, on 11 April 2013, The Garbage Patch State was founded by the artist Maria Cristina Finucci at UNESCO–Paris in front Irina Bokova, the Director General. First of the series of events under the UNESCO patronage and of the Ministry of the Environment, Italy [137]. International organizations have been creating plastic pollution awareness.

June 5 is observed every year as the World Environment Day to increase government action on environmental pressing issues and to raise awareness. In 2018, India hosted the 43rd World Environment Day which had the theme 'Beat Plastic Pollution' with emphasis on disposable or single-use plastics. In India, the Ministry of Environment, Forest and Climate Change invited individuals to take care of their expected social responsibility, urging them to adopt green good deeds in daily life. Many states presented their plans to drastically reduce the use of plastics or ban it completely.

3.7. International, Regional, and Local Banning

In an effort to mitigate plastic pollution problems, many countries all over the world have joined the banning of the use of plastic packages. More countries are expected to join the ban. In 2017, Kenya and Tunisia joined the league of African countries that place a ban on the use of plastic packages. Other countries in Africa include Mali, Cameroon, Uganda, Tanzania, South Africa, etc. Although, most of these countries, like Uganda, are yet to fully implement and enforce the law banning the use of plastic bags. Sadly, Nigeria is yet to look towards this campaign for the plastics ban. In Asia, countries like China, Bangladesh, Cambodia, India, Indonesia, Malaysia, and Taiwan, have either banned or increased taxes on plastic packages. In Europe, the Netherlands, France, UK, Italy, Germany, etc. have either banned or placed taxation on the use of plastic containers. In North and South America, sadly, the United States is yet to put ban on plastic bags into effect. Nevertheless, Mexico, some Canadian provinces, Argentina, Chile, Colombia have taken measures to reduce or discourage the use of synthetic (plastic) packaging materials. The need to place a ban on plastic bags cannot be overemphasized.

3.8. The Use of the Enzymes, PETases

The PETases are esterase class of enzymes which catalyze the hydrolysis of PET (polyethylene terephthalate) plastics to MHET (monomeric mono-2-hydroxyethyl terephthalate). The idealized chemical reaction is (where n = the number of monomers in the chain of polymer) [138]:

$$(\text{ethylene terephthalate})_n + H_2O \rightarrow (\text{ethylene terephthalate})_{n-1} + \text{MHET}$$

Trace amount of the PET degrades to bis(2-hydroxyethyl) terephthalate (BHET). Also, PETases can break down plastics made with PEF (polyethylene-2,5-furandicarboxylate) that is a bioderived replacement of PET. PETases cannot catalyze the hydrolysis of aliphatic polyesters such as polylactic acid or polybutylene succinate [139]. PET non-enzymatic natural degradation will take hundreds of years, but with PETases, it is faster. PET can be degraded by PETases within days.

In 2016, the first PETase was discovered from *Ideonella sakaiensis* strain 201-F6 bacteria found in samples of sludge collected close to a PET bottle recycling site Japan [138, 140] Other types of hydrolases that degrade PET have been reported before this discovery [139]. These include hydrolases such as: esterases, cutinases, and lipases [141]. Discoveries of enzymes that degrade polyesters date as far back as 1975 for α-chymotrypsin and 1977 for lipase, for example.

In the 1970s, PET plastic was put into extensive use and it is suggested that PETases in bacteria evolved recently [138]. PETases may likely have had past enzymatic activity connected with the degradation of waxy coatings on plants.

MHET is degraded in *I. sakaiensis* to ethylene glycol and terephthalic acid by the action of MHETases enzyme.

There were 17 known three-dimensional (3D) crystal structures of PETases as of April 2019. PETase exhibits common qualities with both cutinases and lipases in that it possesses α/β-hydrolase fold; though, the active-site cleft found in PETase is often more open than in the cutinases.

There are roughly 69 PETase-like enzymes including a variety of diverse organisms, and two classifications of these enzymes are type I and type II. It has been suggested that 57 enzymes belong to the type I category while the rest belong to the group of type II, including the PETase enzyme in the *Ideonella sakaiensis.* In all the 69 PETase-like enzymes, the same three residues in the active site exist, suggesting that catalytic mechanism is same in all PETase-like enzymes.

Surface of the PETases double mutant (S131A and R103G) with HEMT (1-(2-hydroxyethyl) 4-methyl terephthalate) attached to its active site. HEMT (1-(2-hydroxyethyl) 4-methyl terephthalate) is an MHET analogue, and has an added methanol esterified to it.

In 2018, some scientists from the University of Portsmouth (UP) with collaboration of the National Renewable Energy Laboratory (NREL) of the US Department of Energy technologically advanced a mutant of this PETase which degrades PET quicker than the natura PETase. Also, in this study it was shown that PETases degrade polyethylene 2,5-furandicarboxylate (PEF). These efforts to mitigate the impacts of plastic wastes are urgently required to protect human, seafood, and our environment [142].

4. Conclusion

There are many ways plastics can influence or interact with wildlife. In the case of microplastics, particles smaller than 4.75 millimeter in diameter, ingestion is the key concern. Consumption of seafood represents one pathway for human exposure to microplastic. One factor which possibly limits the dietary uptake for humans is that microplastics in fish tend to be present in the gut and digestive tract — parts of the fish not typically eaten. Three possible toxic effects of plastic particles are the release of persistent organic pollutant adsorbed to the plastics, leaching of plastic additives, and plastic particles themselves. Biomagnification results from plastic pollution. Due to the usage of chemical additives in plastic production, plastics constitute potential harmful effects which may be carcinogenic or encourage endocrine disruption. Few of the additives are used as brominated flame retardants and phthalate plasticizers. By biomonitoring, chemical additives in plastics, such as phthalates and BPA, have been detected in the human population. Human exposures to these chemicals are through the nose, mouth, or skin. Other additives used are Bisphenol S, Tetrabromobisphenol A**,** Polybrominated diphenyl ethers, etc. All of these additives have been implicated in at least one health issue. There have been substantial efforts to reduce the prevalence of plastic pollution in many areas, through reducing the rate of consumption of plastic and promoting plastic recycling. The use of biodegradable plastics, policymaking, incineration, use of the enzyme PETase, plastic waste collection, promotion of non-usage and lessening usage, and creating awareness, in addition to banning have been the active ways for the management of plastic pollution.

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