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An Urge to Ban the Plasticizer DOP from Pharmaceutical Industries and Health Sector

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Abstract : The packaging business is that the largest and growing shopper of artificial plastics derived from fossil fuels. tho' plastics serve their meant purpose, an outsized proportion finishes up within the atmosphere wherever they persist for hundreds of years. Food and care pharmaceutical packaging plastics account for the majority of plastic waste that area unit polluting the atmosphere. Not solely this, however conjointly the wide used plasticiser Di-Octyl Phthalate(DOP) that renders poly(vinyl chloride) (PVC) soft and malleable will migrate among the fabric and leach out of it over time, ending up within the atmosphere and, frequently, the organic structure. DOP has come back underneath exaggerated scrutiny as its breakdown product area unit believed to be endocrine disruptors and additional noxious than DOP itself. DOP and its breakdown product are known as omnipresent environmental contaminants, and daily human exposure is calculable to be within the metric weight unit per kilogram level. mortals area unit typically exposed to DOP through drinking water, packaged food. Exposure to DOP conjointly happens in hospital environments, wherever DOP leaches directly into liquids that capable PVC/DOP conduit and instrumentality. The latter exposure is at significantly higher levels compared to food and drinking water, specifically putt patients with chronic diseases in danger. This encourages the necessity for different packaging materials therefore avoiding plastic.

Key words- Plasticizer, leaching, health hazards, DOP

I. INTRODUCTION

Usage of non-biodegradable materials for the varied packaging applications has raised environmental pollution considerations [1,2]. Food packaging accounts for the most important growing sector inside the artificial plastic packaging market domain [3–7]. giant amounts of various materials, like paper, glass and plastics, square measure used globally to manufacture packaging materials and over 2 thirds square measure utilized in the food sector alone. This quantity is growing endlessly as a results of changes occurring in habits of food preparation and consumption, also because the positive development of assorted areas and markets within the world [8]. The packaging trade consumes the very best volumes of plastics created globally associated is that the main supply activity waste plastics into the surroundings at an appalling rate [9]. this will be attributed to single-use plastics and also the increase of on-the-go snacks and ready-made meals that imply the once-off use of sturdy plastic packaging material. As a result, there's increasing would like for eco-friendly property packaging materials with the specified physical, mechanical and barrier properties for food packaging.

Several studies have reported on various plasticizers like DOP causing environmental pollution and imposing human health hazards. This review focuses on the ill effects of plasticizers, phthalates and thus plastic, hence encouraging the use of alternative packaging materials like glass as a suitable packaging material in pharmaceutical and health sector.

II. VARIETIES OF PHTHALATES: PHTHALATES AND TEREPHTHALATES

Because of a worldwide increase within the consumption of drinking water (Beverage selling 2011), the materials wont to build these water bottles have come back underneath redoubled scrutiny. Polymers like synthetic resin (PE; employment code no. 2) and synthetic resin terephthalate (PET, additionally referred to as PETE; employment code no. 1) are employed in part of glass, primarily thanks to their rarity and sturdiness. The 2011 nutrient Market Report according that "plastic packaging is most popular over shut in nearly each country" which "PET is that the most dynamic and quickly growing segment" (Beverage selling 2011). PET could be a polyester that's made either from the esterification reaction of terephthalic acid with ethanediol and resulting chemical action or, or else, by the transesterification of dimethyl terephthalate with ethanediol and resulting chemical action. Once polymerized, the ensuing polyester could be a arduous and rather brittle material. the sole suggests that by that some terephthalic acid, or associate degree organic compound of it, may leach from it's by gradual depolymerization of the chemical compound chains forming the fabric.

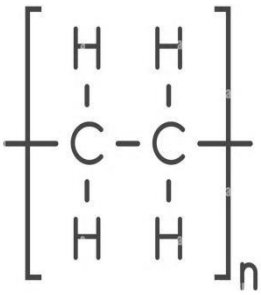

Fig. 1: polyethylene – PE

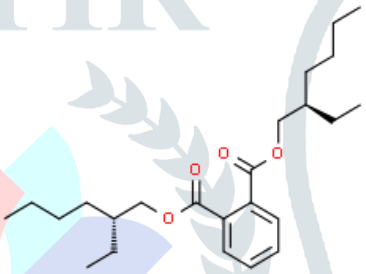

Fig. 2: Di-Octyl Phthalate

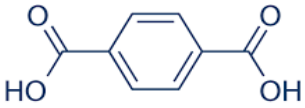

Fig. 3: Terepthalic acid

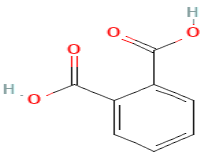

Fig. 4: Phthalic acid

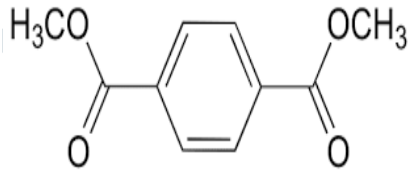

Fig. 5: Dimethyl terepthalate

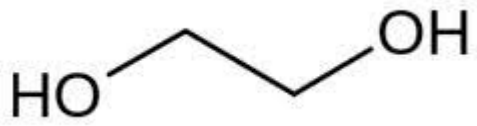

Fig. 6: Ethylene glycol

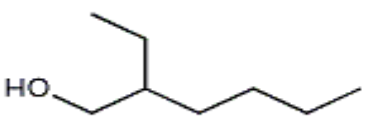

Fig. 7: 2-Ethyl hexanol

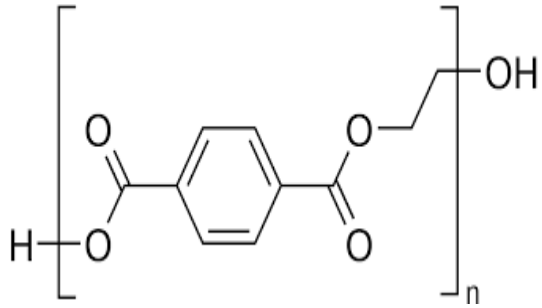

Fig. 8: Polyethylene terephthalate- PET

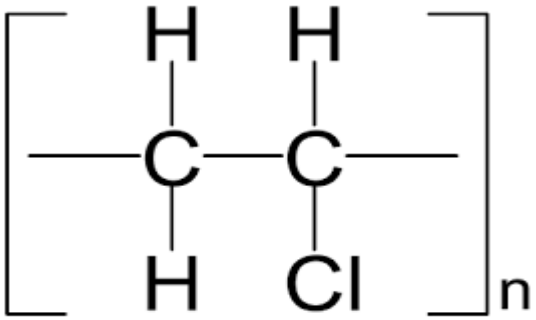

Fig. 9: poly (vinyl chloride) - PVC

Esters of phthalic acids (Phthalate) are the class of xenobiotic organic compounds, extensively used for the synthesis of plastic products and also to make them more flexible. These are not chemically bound to plastics; so they can easily leach out from it and get mixed up with the surrounding environment [10,11]. Medical devices such as tubing, feeding bags, external nutrition, peritoneal dialysis bags, infusion tubing, oxygen masks, blood bags and catheters are manufactured by polyvinyl chloride (PVC) that contains an average 20–40% DOP by mass [12,13]. Phthalates are used to upcline transparency, and durability of PVC materials since 1930s.

In the ortho position, phthalates have a long alkyl side-chain likely for developmental and reproductive hazardous impacts in living organisms. The order of toxic potential of Phthalate is DOP>DBP>BBP in addition to DiNP, DnHP, and DiBP [14]. The DOP is the most common plasticizer that is not covalently attached to plastic material and can be released out from the product polluting the outer atmosphere. DOP exposures from many sources through food appear to be the nearest to the bearable every day consumption of 2 mg/day in inhabitants [15]. However, when an individual goes through specific medical treatment, he may be exposed to greater quantity of DOP via medical apparatus and PVC [16]. Inhalation, ingestion and dermal absorption are the different processes through which humans are exposed on a routine basis [17,18]. In addition, patients are highly exposed to these phthalates and DOP containing medical devices [19].

When phthalates are released in the aquatic environment, they may change into other forms with this human health and aquatic ecosystem which are exposed to unknown risk [20]. As compared to adults, children are highly exposed to DOP [21,22]. Phthalates are known as the EDCs [23]. The developing fetus is exposed to EDCs on breast feeding and through placenta [24,25]. Moreover, prenatal phthalate exposure has been recommended to reduce child mental/motor development and raise internalizing behavior throughout the preschool time [26]. The exposure to phthalates cause the threat from allergic diseases which include eczema and asthma. This review is focused on the recent reports and evidences regarding the leaching of phthalate from medical devices, their toxicity, leaching, and exposure and health impacts as derived from relevant literature.

III.TOXIC EFFECTS OF PHTHALATE

In New York city, 295 children were investigated and showed relationship between neonatal behavior and prenatal maternal urinary concentrations of Phthalate metabolites and their result reported the relationship among neurological effect and prenatal Phthalate exposure in animals or human beings [27]. In addition, a researcher studied infusion system containing the DOP and the authors determined that by using DOP – plasticized PVC infusion systems for total parental nutrition that increased the risk for cholestasis and showed the various toxic effects over different organ systems including liver in humans and animals [28]. The research work was carried out over the mice. The results showed that DOP induced hepatic Tumorigensis through a peroxime proliferator – activated receptor a – in depended (PPARa) while DOP caused the liver tumorigensis [29]. The authors recommended that DOP induced which increased the oxidative stress and caused the inflammation or the expression of protooncogenes and resulted in the tumorigensis in PPARa –null mice.

- **Neurological effects**

A study found that acute postnatal exposure to DOP has a negative influence on hippocampus development in male rats [30]. The researchers discovered that exposing male rats to (DOP; 10 mg/kg, i.p.) from p16 to p22 reduced axonal markers in the CA3 distal stratum oriens and decreased the density of undeveloped and mature neurons in the dentate gyrus and CA3, respectively, and the same marker was found in the hippocampus of female rats in saline and DOP treated animals. Prenatal Phthalate exposure may increase the chance of neurodevelopment damage, according to animal studies [31].The study of elucidating the links between EDCs and neurodevelopment, carried out by Schug and the authors found that with the exposure of EDCs through phthalates alter the brain function in children and disease susceptibility later in life [32].

- **DNA damage**

The neutral comet assay was used to investigate the Phthalate and the link between Phthalate exposure in the environment and deoxyribos nucleic acid (DNA) damage in human sperm. The author (Duty et al. 2003) demonstrated that urine MEP at ambient levels is linked to increased DNA damage in sperm in the first human data. Furthermore, a study on DNA damage in human sperm was undertaken by a researcher, and the authors discovered that DOP is connected to greater DNA damage in a group of males exposed to DOP, and another study was conducted by a researcher, which revealed that DEP exposure increased DNA damage in sperm [33].

- **Oxidative stress**

Phthalate and DBP have been linked to increased brain neurotoxicity. The aetiology of neurological illnesses and neurobehavioral alterations was recently discovered by a researcher [34]. The scientists discovered that oxidative damage may mediate the neurobehavioral alterations in the brain of mice produced by DBP, and that co-administration of Mangiferin (MAG, 50 mg/kg/day) may protect the brain from oxidative damage caused by DBP exposure. DBP at higher dosages (25 or 125 mg/kg/day) causes oxidative stress in the mouse brain, exposing the link between oxidative stress and behaviour such as anxiety. The effect of intravenous lipid infusion on blood levels of malondialdehyde, which is produced by free radical-induced polyunsaturated fatty acid breakdown, was investigated in 7 newborns and a group of children receiving hyperalimentation via PVC tubing while on cyclic parenteral feeding [35]. The radicals of oxygen are the major contributors to tissue damage during inflammation, and DOP has revealed an increase in oxidative stress, but MEHP boosted the formation of H2O2 in neutrophils [36].

- **Effect on lungs**

[37] Conducted research on the impact of DOP on cell proliferation and tissues in the lungs of baby rats. In his studies, DOP was given to female rats in the final days of pregnancy, and the author analysed at different periods of 2, 7, and 14 days postnatally, encompassing the entire period of alveolarization; while lung histology showed the swelling of air spaces and decrease of respiratory surface region, and the authors researched over the perinatal exposure of DOP that leads to delayed lung maturation and limited growth in newborn rats, the authors discovered that the maximum dose of DOP (750 mg) caused delayed lung maturation and limited [38]. A prior study published his findings on the risk of Phthalate exposure from PVC material in the expansion of allergies, asthma, meta-analysis, and systematic review [39]. The scientists discovered that Phthalate exposure from PVC products causes asthma in children, and epidemiologic investigations in children revealed links between household markers of Phthalate exposure and the risk of allergies and asthma. Children's wheezing, asthma, and rhinitis may be linked to higher levels of DOP and BBP in house dust [40,41].

- **Reproduction effects**

DOP reduces testicular weight and sperm production and contributes to seminiferous tubule atrophy, which leads to infertility and damages liver, kidney, thyroid, and spleen cancer in male mice [42]. During a scholar's study of laboratory rats, it was discovered that Phthalate is responsible for the decreased production of estradiol, a sex hormone that is primarily responsible for the growth of reproductive organs

in females, and that Phthalate exposure leads to disorders in the development of reproduction and testicular dysgenesis in humans [43].

- **Effects over liver**

A researcher conducted studies on the Reexamination of the PPAR-activation mode of action as a foundation for analysing human cancer risks of atmospheric pollutant [44,45], which included liver tumours in mice and rats, as well as leydig cells and pancreas cells creating tumours in rats. Finally, the authors discovered that DOP causes liver cancers in rodents that are dependent on PPAR activation, but that this is unrelated to humans. Not only this but also a researcher conducted a study regarding the DOP creating hepatic tumorigenesis with a peroxisome proliferator-activated receptor, alpha-independent pathway and the authors determined through their two studies that liver tumors are produced by DOP in mice and liver tumors may be produced by alternative mechanism.

- **Gastrointestinal effects**

In 2009, a researcher published a report claiming that "the use of DOP held by infusion systems elevated the risk of cholestasis" over two to three years. The author discovered that using plasticized DOP PVC infusion systems for total parental nutrition (TPN) increased the incidence of cholestasis by 5.6; however, using free DOP infusion systems for TPN is recommended, especially in babies.

IV.LEACHING STUDIES

The presence of DOP in peritoneal dialysis equipment such as bags and tubing was found in leaching tests of adult patients undergoing peritoneal dialysis and parental nourishment. Peritoneal dialysis solution was retained in the tested PVC bag, which had less 3.72g dm-3, and infusion bottles made of low-density polyethylene (LDEP) contained less DOP than PVC bags.

Ringer's solution made by LDEP exposed more DOP than LDEP bottles used for packaging physiological saline solution (0.9 percent NaCl). DOP concentrations were 17.30 and 5.83 gdm3 in physiological saline and Ringer's solution, respectively. After that, a researcher looked into Phthalate leaching studies [46].

The authors demonstrated the amount of Phthalate leached from medical equipment used in artificial nourishment and infusion processes, such as DOP, DEHT, DINCH, and TOTM. Phthalate migration investigations were conducted at a temperature of 40°C with time intervals of 1 day, 3 days, and 10 days. With the passage of time, the maximum migration of Phthalate increased. The leaching of Phthalate and its metabolites from 32 premature newborns, 20 with birth weights of less than 1500 g and 12 with birth weights of more than 2500 g, was studied at a Taiwanese neonatal critical care unit. [47].

The scientists used Tendam mass spectrometry, reversed phase high performance liquid chromatography, and atmospheric pressure chemical ionisation to determine three DOP metabolites in their urine samples. They used an orogastric tube, nasogastric tube, and endotracheal tube to treat medium levels of DOP metabolites, and the results were much better than those who did not use an orogastric tube, nasogastric tube, and endotracheal tube. The median level of DOP after intravenous injections was less than 2-fold higher than healthy people who did not get intravenous injections ($p = 0.01$).

The median amount of Phthalate metabolite in low birth neonates was found to be similar. Rose et al. (2012) have also determined the amount of DOP leached from infusion sets, Mediplus TIVA, non-lipid, and lipid infusates. At 24oC, 32oC, and 37oC, solutions were infused through TIVA sets at 12 ml.h-1 for 6 hours at 24oC, 32oC, and 37oC, and TIVA sets were filled with two ml infusates, incubated, and sealed at 24 and 37oC. Phthalate was measured in all lipid infusates after dynamic and static contact.

Because of their small body mass and the numerous medical devices connected with DOP exposure, a researcher has observed Phthalate leaching from medical devices loaded with medicinal solution during infants. Temperature, storage period, the amount of DOP present in devices, shaking of devices while in contact with medical solution, and the degree of PVC degradation were all factors in the authors' findings.

The amount of Phthalate leached out of the 78 blood bags made in Japan, according to a study. DOP and MEHP were directly determined by LC–MS and on-line extraction [48]. When compared to other blood products, PVC bags leached the most, about 0.7 mg/kg weight/time. A researcher extracted leached DOP from PVC tubing using an aqueous solution of polysorbate 80 (Tween 80). The authors discovered

that increased temperature and circulation velocity increased the amount of DOP released, and that the diffusion coefficients at 5 and 40 oC were 9.1 and 156.0 [49].

V.CONVENTIONAL ALTERNATIVE PACKAGING MATERIALS

As plasticizers leach out into the plastic containers causing contamination of the product which on ingestion leads to adverse health hazards, some alternative packing materials have been suggested as follows:

- **Glass Packaging**

A borosilicate glass with considerable concentrations of boric oxide, aluminium oxide, and alkali or alkaline earth oxides is known as neutral glass. It has excellent hydrolytic and thermal shock resistance. Glass is a popular packaging material because it can be moulded into any form, size, or thickness. Glass is used in the majority of parenteral formulations.

They are clear or uncolored packaging that allows for visual inspection of the contents. They provide excellent powder protection because powder is extremely sensitive to moisture and temperature. It comes in a range of forms and sizes to suit your needs. Amber-colored glass is frequently utilised in the packaging of more delicate items.

However glass has some disadvantages. It possesses high risk during the transport and handling as it is fragile in nature.[50]

- **Rubber Packaging**

Rubber is mostly utilised to make vial closures, transfusion fluid bottles, falling bottles, and washers for a variety of other products. Natural rubber, neoprene, nitrile, butyl chlorobutyl, bromobutyl, and silicone are the most common forms of rubber used in pharmaceutical products. Silicone is the most expensive and, although being the most inert, is easily permeable to moisture, gases, and preservatives.

Rubber is excellent because it has a low water absorption rate, making it more resistant to moisture and humidity. It is simple to handle and transport due to its stretchy nature. When compared to metal and glass, it is the less expensive option. It has a good financial worth. The closing apparatus is mostly made of rubber, which provides further protection against contamination. Because of the presence of the nitrile group, nitrile rubber is heat and grease resistant. [51]

Rubber, on the other hand, has several drawbacks. In the case of rubber, bactericide absorption and extractive leaching occur in significant amounts. When exposed to chemical compounds, it does not operate properly. It is really costly. Rubber material can sometimes react with the product, changing its physical and chemical qualities.

- **Metal Packaging**

Metal is one of the most common materials used to package hazardous compounds. Aluminium foil, tin plated steel, lead, and other metals are often used for this purpose. The majority of collapsible tube packaging is made of metal. The term "canning" is commonly used to describe this technique. During the last century, canned food has become a major part of the human diet in developed countries.

Because metal is impermeable to light, moisture, and gases, it provides a high level of environmental protection. Additionally, because metal is hard, it is not easily broken, making it easier to transport and handle. When compared to glass containers, they are far lighter. Metal surfaces can simply be printed with attractive labels.

Well some of the shortcomings of Metal containers are that they show high economical value. They are heavy in weight which may be create a little hindrance in transportation. Some metals are react with the products making it poisonous. Rusting can cause in some metals due to absorbance of the moisture.[52]

Packaging Interventions:

Packaging Material	Advantages	Disadvantages
Glass	Transparent or uncoloured packaging to permit the visual inspection of the product contents. Good protection for powder because powder is very sensitive against the moisture and temperature. Available in variety of shapes and sizes according to the needs. Amber coloured glass is also used in the packaging for the more sensitive materials.	High risk during the transport and handling as it is fragile in nature. Heavy in weight. Risk of product contamination due to broken glass pieces and sometimes may release alkali to aqueous preparation.[53]
Rubber	Water absorption is very low, so it provides the better resistance against the moisture and humidity. Its stretchable nature makes it is easier for handling and transportation. Cheap. Rubber materials used for closing apparatus provide additional protection against any contamination. Nitrile rubber is heat and oil resistant.	Does not perform well when exposed to the chemicals substances. Very expensive. Sometimes rubber materials also react with the product and alter the product's physical and chemical properties.[54]
Metal	Provides high degree of protection against light, moisture and gases. Unbreakable, easy to transport and handle. Light weight. Attractive labels	High economic value. Some metals reacts with the products causing poisonous reactions. Rusting in some metals.[55]

Table 1: Types of Packaging

VI. LETRATURE REVIEW:

1. Hanno C Erythropel et, al. Review that plasticizers can migrate within the material and leach out of it over time, ending up in the environment and, frequently, the human body.The objective of this review is to summarize and comment on published sources of DOP exposure and to give an overview of its environmental fate. Exposure through bottled water was examined specifically, as this concern is raised frequently, yet only little exposure to DOP occurs through bottled water, and DOP exposure is unlikely to stem from the packaging material itself. Packaged food was also examined and showed higher levels of DOP contamination compared to bottled water. Exposure to DOP also occurs in hospital environments, where DOP leaches directly into liquids that passed through PVC/DOP tubing and equipment. The latter exposure is at considerably higher levels compared to food and bottled water, specifically putting patients with chronic illnesses at risk.

2. Joel A Tickner et,al. observed toxicity of DOP and availability of alternatives to many DOP-containing PVC medical devices presents a compelling argument for moving assertively, but carefully, to the substitution of other materials for PVC in medical devices. The substitution of other materials for PVC would have an added worker and community health benefit of reducing population exposures to DOP, reducing the creation of dioxin from PVC production and disposal, and reducing risks from vinyl chloride monomer exposure.

3. EDS Van Vliet et, al. point out two alternative approaches are available for replacing DOP in NICU medical products:(1) replacement by DOP-free plasticizers; and (2) replacement of PVC entirely through the use of other polymers. Both approaches seem to provide less harmful substitutes to DOP, but support

PVC-free polymers as the preferred alternative. However, significant data gaps exist, particularly for the alternative polymers. In all, 10 out of 21 (48%) products in the NICU audit were DOP-free; six consisted of alternative polymers and four of alternative plasticizers. Of the remaining 11 products, only three were available without DOP at the time of the audit.

4. L Bernard et. Al. Development Analytical method to assess the risk to patients of DOP plasticizer alternatives, reliable analytical methods must be first developed in order to generate data that supports clinical studies being conducted in this area. After a brief introduction of the characteristics and toxicity of the selected plasticizers used currently in MDs, this review outlines recently analytical methods available to determine and quantify these plasticizers in several matrices, allowing the evaluation of potential risk and so risk management.

Sandra S Hil et. Al. Studied and work for extensive review of existing research, the Panel concluded that there was not enough evidence of harmful health effects to remove di-(2-ethylhexyl) phthalate (DOP) and other plasticizers from use in medical tubing. The Panel recognized the importance of plasticizers in enabling tubing such as PVC for respiratory support or in dialysis to be flexible enough for use in a variety of clinical applications that might not be possible with rigid (plasticizer-free) tubing. Nevertheless, we reviewed the literature regarding the health effects for five of the most common compounds, plasticizers and antioxidants found in medical tubing, and suggest that further clinical studies be conducted. We concur with the Panel′s recommendation that alternative materials be developed and studied.

Federica Chiellini et. Al. Outlines the scientific approaches for preventing DOP contamination of humans by P-PVC medical devices, highlighting the impact of the proposed alternative materials on human health and strategies for implementing them.

Alternative Plasticizers:

Alternative	**Function/Product**	**Human Health Concerns**	**Environmental Concerns**
ATBC: Acetyl tributyl citrate	• Primarily used as a plasticizer in cosmetic products, toys, vinyl, adhesives, medical devices, pharmaceutical tablet coatings, food packaging, flavoring substance in foods, printing inks and plastics in concrete. • Also used as a surface lubricant in the manufacture of metallic articles that contact food. [60, 61, 63, 65, 21]	• Intravenous exposure affects the central nervous system and blood in laboratory animals. May have moderate irritation effects on eyes and increase liver weights.[66] • Studies show that it inhibits the proliferation of Lymph node T cells [62] • Exhibits fire and explosive hazard in the presence of strong oxidizers and nitrates [60]	Can bioaccumulate and is inherently biodegradable (in an inherent biodegradation test, 80 percent was degraded). However, in a nonstandard test aerobic degradation was slow and no data is available on anaerobic degradation . [66]
DINCH: Di-isononylcyclohexane-1, 2-dicarboxylate	Primarily used as a plasticizer in PVC medical devices (blood tubes or packaging for nutrient solutions), toys, food packaging, cosmetics products, shoes, exercise mats and cushions, textile coatings, printing inks [63].	Acute toxicity effect is low. However, an increase in testes weight, liver weight, thyroid weight, serum gammaglutamyl transferase and thyroid-stimulating hormone was observed in laboratory animals after repeated exposure. Blood and transitional epithelium cells in urine was also observed [67, 71].	No data found regarding effects of environmental exposures.
DOTP: Dioctyl terephthalate	Primarily used as a plasticizer for PVC toys, childcare articles, consumer products, beverage closures and other polymer materials including cellulose acetate-butyrate,	Slightly irritating to eyes but will not damage eyes. • Prolonged exposure may cause dermatitis. Studies involving rodents showed inflammatory damage	Potential for bioconcentration in aquatic organisms is low. Likely to be biodegradable under aerobic and anaerobic conditions [70].

	cellulose nitrate, and chloroprene rubbers [70,71].	to the kidneys [68].	
ESBO: Epoxidized soybean oil	Primarily used as a plasticizer in closure gaskets used to seal glass jars, and as a stabilizer to minimize the ultraviolet degradation of PVC resins baby food jars, fillers, paint and lacquers, adhesives, printing inks, and packaging [64,66].	A worker developed asthma from exposure to vapors from heated PVC film. Vapor may also produce asthmatic symptoms in as little as 5 minutes [66]. • Studies involving rats have reported skin and eye irritations, secondary agent in bronchospastic reaction. • Suspected to cause some effects on the kidney, liver, testis and uterus by repeated oral administration [64].	Toxic to the crustacean Daphnia magna. Estimated to be bioaccumulative. Two standard tests administered by OECD concluded it is biodegradable in aerobic environments [66].
Mesamoll II: alkyl sulphonic phenyl ester (ASE)	Used as a plasticizer in PVC, polyurethanes, natural rubber, styrene-butadiene rubber, blends of styrene butadiene rubber and butadiene rubber, isobutylene isoprene rubber, acrylonitrile butadiene rubber, and chloroprene rubber [69].	Has not been comprehensively studied for toxic effects.	No data found regarding effects of environmental exposures.
TETM: Tri-2-ethyl hexyl tri-mellitate	Primarily used for heat resistant PVC articles, PVC-products used in the hospital sector (blood platelet bags), packing, cables, profiles, and floor/ wall coverings [66]	May cause irritation, nausea and vomiting in humans from exposure to mists and fumes. • Toxic to laboratory animals through inhalation. • Shown to irritate the skin of guinea pigs, rabbits and mice and the eyes of rabbits. • Studies in dogs showed an increase in weight of liver and spleen. • In rats, exposure through diet resulted in slightly increased liver weights and peroxisome proliferation [66].	Very limited data on environmental effects is available. • Potential for environmental effects is associated with the accumulation of the compound in biota, in aquatic sediments and in soils treated with sewage sludge. • Available data indicate that it does not biodegrade readily [66].
COMGHA: Acetylated monoglycerides of fully hydrogenated castor oil	Used in PVC-containing films, tubes, bottles, food packaging materials and other polymers such as polyolefin, styrene, and PET [71].	No data found describing human exposure. • Slightly lower migration rate was found when compared to DOP [71].	• No data found regarding potential environmental effects.

Table 2: Alternative Plasticizers

CONCLUSION

No doubt plastic is the most convenient and widely used packaging material due to its light weight and ease of transportation. However plastics pose a high risk to human beings and nature. The plasticizers like DOP leach into the product from the containers contaminating the product thus producing toxic effects. The alarming effects of plasticizers encourage one to discover such plasticizers that won't leach into the container till then one should avoid using plastic as a preferable packaging material but; as study shows PVC packaging can be interacted with formulation sited with DOP in but the formulation. API did not participate in leaching of phthalates, but the non-ionic surfactants used in the formulation foot forward

and take participation leaching of phthalates and can lead to phthalate poisoning. So as the letrature study shows the phthalate can induce liver as well as cardio toxicity and can also lead to urologic, genital and endocrine disorders.

REFERENCES:

1. Khalil, H.A.; Davoudpour, Y.; Saurabh, C.K.; Hossain, M.S.; Adnan, A.; Dungani, R.; Paridah, M.; Sarker, M.Z.I.; Fazita, M.N.; Syakir, M. A review on nanocellulosic fibres as new material for sustainable packaging: Process and applications. Renew. Sustain. Energy Rev. **2016**, 64, 823–836. [CrossRef]
2. Nurul, M.F.; Jayaraman, K.; Bhattacharyya, D.; Mohamad, M.H.; Saurabh, C.K.; Hussin, M.H.; HPS, A.K. Green composites made of bamboo fabric and poly (lactic) acid for packaging applications—A review. Materials **2016**, 9, 435. [CrossRef]
3. Attaran, S.A.; Hassan, A.;Wahit, M.U. Materials for food packaging applications based on bio-based polymer nanocomposites: A review. J. Thermoplast. Compos. Mater. **2015**, 30, 143–173. [CrossRef]
4. Cazón, P.; Velazquez, G.; Ramírez, J.A.; Vázquez, M. Polysaccharide-based films and coatings for food packaging: A review. Food Hydrocoll. **2017**, 68, 136–148. [CrossRef]
5. Chiellini, E. Environmentally Compatible Food Packaging; Woodhead Publishing: Cambridge, UK, 2008.
6. Ignatyev, I.A.; Thielemans, W.; Vander Beke, B. Recycling of polymers: A review. ChemSusChem **2014**, 7, 1579–1593. [CrossRef]
7. Muller, J.; Martínez, C.G.; Chiralt, A. Combination of poly (lactic) acid and starch for biodegradable food packaging. Materials **2017**, 10, 952. [CrossRef] [PubMed]
8. Piergiovanni, L.; Limbo, S. Food Packaging Materials; Springer: Basel, Switzerland, 2016.
9. De Kock, L.; Sadan, Z.; Arp, R.; Upadhyaya, P. A circular economy response to plastic pollution: Current policy landscape and consumer perception. S. Afr. J. Sci. **2020**, 116, 1–2. [CrossRef]
10. Pradeep, S., Benjamin, S. 2012. Mycelial fungi completely remediate Di-Octyl Phthalate, the hazardous plasticizer in PVC blood storage bag. Journal of hazardous materials, 235, 69-77.
11. Surhio, M.A., Talpur, F.N., Nizamani, S.M., Talpur, M.K., Afridi, H.I., Khaskheli, A.A. 2017a. Leaching of phthalate esters from different drinking stuffs and their subsequent biodegradation. Environmental Science and Pollution Research, 24(22), 18663-18671.
12. Guo, Z., Wang, S., Wei, D., Wang, M., Zhang, H., Gai, P. 2010. Development and application of a method for analysis of phthalates in ham sausages by solid-phase extraction and gas chromatography–mass spectrometry. Meat science, 84(3), 484-490.
13. Liu, H.C., Den, W., Chan, S.F., Kin, K.T. 2008. Analysis of trace contamination of phthalate esters in ultrapure water using a modified solid-phase extraction procedure and automated thermal desorption–gas chromatography/mass spectrometry. Journal of Chromatography A, 1188(2), 286-294.
14. Fabjan, E., Hulzebos, E., Mennes, W., Piersma, A.H. 2006. A category approach for reproductive effects of phthalates. Critical reviews in toxicology, 36(9), 695-726.
15. Lyche, J.L., Gutleb, A.C., Bergman, Å., Eriksen, G.S., Murk, A.J., Ropstad, E. 2009. Reproductive and developmental toxicity of phthalates. Journal of Toxicology and Environmental Health, Part B, 12(4), 225-249.
16. Kamrin, M.A. 2009. Phthalate risks, phthalate regulation, and public health: a review. Journal of Toxicology and Environmental Health, Part B, 12(2), 157-174.
17. Halden, R.U. 2010. Plastics and health risks. Annual review of public health, 31, 179-194.
18. Heudorf, U., Mersch-Sundermann, V., Angerer, J. 2007. Phthalates: toxicology and exposure. International journal of hygiene and environmental health, 210(5), 623-634.
19. Koch, H.M., Bolt, H.M., Preuss, R., Angerer, J. 2005. New metabolites of Di-Octyl Phthalate (DOP) in human urine and serum after single oral doses of deuterium-labelled DOP. Archives of toxicology, 79(7), 367-376.
20. Huang, J., Nkrumah, P.N., Li, Y., Appiah-Sefah, G. 2013. Chemical behavior of phthalates under abiotic conditions in landfills. In Reviews of Environmental Contamination and Toxicology Volume 224 (pp. 39-52): Springer.
21. Hellerstedt, W.L., McGovern, P.M., Fontaine, P., Oberg, C.N., Cordes, J.E. 2008. Prenatal environmental exposures and child health: Minnesota's role in the National Children's Study. Minnesota medicine, 91(9), 40-43.

22. Wittassek, M., Angerer, J., Kolossa-Gehring, M., Schäfer, S.D., Klockenbusch, W., Dobler, L. 2009. Fetal exposure to phthalates–a pilot study. International journal of hygiene and environmental health, 212(5), 492-498.
23. Ponzo, O.J., Silvia, C. 2013. Evidence of reproductive disruption associated with neuroendocrine changes induced by UV–B filters, phtalates and nonylphenol during sexual maturation in rats of both genders. Toxicology, 311(1-2), 41-51.
24. Hines, E.P., Calafat, A.M., Silva, M.J., Mendola, P., Fenton, S.E. 2009. Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. Environmental health perspectives, 117(1), 86.
25. Latini, G., Wittassek, M., Del Vecchio, A., Presta, G., De Felice, C., Angerer, J. 2009. Lactational exposure to phthalates in Southern Italy. Environment international, 35(2), 236-239.
26. Whyatt, R.M., Liu, X., Rauh, V.A., Calafat, A.M., Just, A.C., Hoepner, L. 2012. Maternal prenatal urinary phthalate metabolite concentrations andchild mental, psychomotor, and behavioral development at 3 years of age. Environmental health perspectives, 120(2), 290.
27. Engel, S.M., Zhu, C., Berkowitz, G.S., Calafat, A.M., Silva, M.J., Miodovnik, A. 2009. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. Neurotoxicology, 30(4), 522-528.
28. von Rettberg, H., Hannman, T., Subotic, U., Brade, J., Schaible, T., Waag, K.L. 2009. Use of Di-Octyl Phthalate–containing infusion systems increases the risk for cholestasis. Pediatrics, 124(2), 710-716.
29. Ito, Y., Yamanoshita, O., Asaeda, N., Tagawa, Y., Lee, C.H., Aoyama, T. 2007. Di-Octyl Phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. Journal of Occupational Health, 49(3), 172-182.
30. Smith, C., Macdonald, A., Holahan, M. 2011. Acute postnatal exposure to Di-Octyl Phthalate adversely impacts hippocampal development in the male rat. Neuroscience, 193, 100-108.
31. Miodovnik, A., Edwards, A., Bellinger, D.C., Hauser, R. 2014. Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. Neurotoxicology, 41, 112-122.
32. Schütze, A., Gries, W., Kolossa-Gehring, M., Apel, P., Schröter-Kermani, C., Fiddicke, U. 2015. Bis-(2-propylheptyl) phthalate (DPHP) metabolites emerging in 24 h urine samples from the German Environmental Specimen Bank (1999–2012). International journal of hygiene and environmental health, 218(6), 559-563.
33. Hauser, R., Meeker, J., Singh, N., Silva, M., Ryan, L., Duty, S. 2006. DNA damage in human sperm is related to urinary levels of phthalate
monoester and oxidative metabolites. Human Reproduction, 22(3), 688-695.
34. Yan, B., Guo, J., Liu, X., Li, J., Yang, X., Ma, P. 2016. Oxidative stress mediates dibutyl phthalateinduced anxiety-like behavior in Kunming mice. Environmental toxicology and pharmacology, 45, 45-51.
35. Kambia, N., Dine, T., Gressier, B., Frimat, B., Cazin, J.-L., Luyckx, M. 2011. Correlation between exposure to phthalates and concentrations of malondialdehyde in infants and children undergoing cyclic parenteral nutrition. Journal of Parenteral and Enteral Nutrition, 35(3), 395-401.
36. Vetrano, A.M., Laskin, D.L., Archer, F., Syed, K., Gray, J.P., Laskin, J.D. 2010. Inflammatory effects of phthalates in neonatal neutrophils. Pediatric research, 68(2), 134.
37. Rosicarelli, B., Stefanini, S. 2009. DOP effects on histology and cell proliferation in lung of newborn rats. Histochemistry and cell biology, 131(4), 491-500.
38. Chen, S.Q., Chen, J.N., Cai, X.H., Chen, G.R., Gao, Y., Ge, R.S. 2010. Perinatal exposure to di-(2-ethylhexyl) phthalate leads to restricted growth and delayed lung maturation in newborn rats. Journal of perinatal medicine, 38(5), 515-521.
39. Jaakkola, J.J., Knight, T.L. 2008. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. Environmental healthperspectives, 116(7), 845.
40. Bornehag, C., Nanberg, E. 2010. Phthalate exposure and asthma in children. International journal of andrology, 33(2), 333-345.
41. Kolarik, B., Naydenov, K., Larsson, M., Bornehag, C.G., Sundell, J. 2008. The association between phthalates in dust and allergic diseases among Bulgarian children. Environmental health perspectives, 116(1), 98.
42. Ventrice, P., Ventrice, D., Russo, E., De Sarro, G. 2013. Phthalates: European regulation, chemistry, pharmacokinetic and related toxicity. Environmental toxicology and pharmacology, 36(1), 88-96.

43. Eveillard, A., Mselli-Lakhal, L., Mogha, A., Lasserre, F., Polizzi, A., Pascussi, J.-M., et al. (2009). Di-(2-ethylhexyl)-phthalate (DOP) activates the constitutive androstane receptor (CAR): a novel signalling pathway sensitive to phthalates. Biochemical pharmacology, 77(11), 1735-1746.
44. Barr, D.B., Breysse, P.N., Chapin, R., Marcus, M. 2006. NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di-Octyl Phthalate. Reproductive toxicology, 22, 291-399.
45. Guyton, K.Z., Chiu, W.A., Bateson, T.F., Jinot, J., Scott, C.S., Brown, R.C. 2009. A reexamination of the PPAR-α activation mode of action as a basis for assessing human cancer risks of environmental contaminants. Environmental health perspectives, 117(11), 1664.
46. Bernard, L., Cueff, R., Bourdeaux, D., Breysse, C., Sautou, V., Group, A.S. 2015. Analysis of plasticizers in poly (vinyl chloride) medical devices for infusion and artificial nutrition: comparison and optimization of theextraction procedures, a pre-migration test step. Analytical and bioanalytical chemistry, 407(6), 1651-1659.
47. Su, P.H., Chang, Y.Z., Chang, H.P., Wang, S.L., Haung, H.I., Huang, P.C. 2012. Exposure to Di-Octyl Phthalate in premature neonates in aneonatal intensive care unit in Taiwan. Pediatric Critical Care Medicine, 13(6), 671-677.
48. Inoue, K., Kawaguchi, M., Yamanaka, R., Higuchi, T., Ito, R., Saito, K. 2005. Evaluation and analysis of exposure levels of di (2-ethylhexyl)phthalate from blood bags. Clinica Chimica Acta, 358(1-2), 159-166.
49. Takehisa, H., Naoko, E., Masahiko, S., Katsuhide, T., Moriyuki, O., Keizoh, S. 2005. Release behavior of diethylhexyl phthalate from the polyvinyl-chloride tubing used for intravenous administration and the plasticized PVC membrane. International journal of pharmaceutics, 297(1-2), 30-37.
50. Council of Europe, European Pharmacopoeia, 5th ed., Strasbourg: Council of Europe, 2004.
51. Jenke DJ et al. Pharm Sci Technol, 2002; 56:332-71.
52. Mehta R.M. Dispensing Pharmacy, Containers and closures for dispensed products. (4th ed.), Delhi, Vallabh Prakashan, 2009; 49-50.
53. Kunal C M, Akhilesh D, Kumar B. Recent Trends in Pharmaceutical Packaging: A Review. International Journal Of Pharmaceutical And Chemical Sciences, 2012; 1(3): 933-934.
54. Singh A, Sharma P.K, Malviya R: Eco Friendly Pharmaceutical Packaging Material. World Applied Sciences Journal, 2011; 14(11): 1703-1716.
55. Mehta K, Akhilesh D and Shyam KB: Recent trends in pharmaceutical packaging: A review. International Journal of Pharmaceutical and Chemical Sciences, 2012; 1(3): 933-943.
56. Pilchik R: Pharmaceutical Blister Packaging, Part I: Rationale and Materials. Pharm Technol, 2000; 24(11): 68-78.
57. United State Pharmacopoeia. Appendices. pp.no. 2653, 2654, 2558, 2580.
58. Indian Pharmacopoeia. Vol I. The Controller of Publication. New Delhi, 1996; 9-10.
59. Cooper and Gunn's. Tutorial pharmacy. Edited by Carter SJ. Delhi: CBS publisher &distributors, Delhi. 6th edition, 2005.
60. Johnson, W. Jr. (2002). Final Report on the Safety Assessment of Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Trihexyl Citrate, and Acetyl Trioctyl Citrate. International Journal on Toxicology, 21: 1-17.
61. U.S. EPA High Production Volume (HPV) Chemicals Challenge Program. (2003). Assessment of Data Availability and Test Plan for Acetyl Tributyl Citrate (ATBC). Available at www.epa.gov/HPV/pubs/summaries/acetlcit/ c15025tp.pdf
62. Nara, K., Nishiyama, K., Natsugari, H., Takeshita, A., and Hideyo Takahashi. 2009. Leaching of the Plasticizer Acetyl Tributyl Citrate (ATBC) from Plastic Kitchen Wrap. Journal of Health Sciences, 55(2): 281-284.
63. ChemSystems. (2008). Process Evaluation/Research Program: Development of Non-Phthalate Plasticizers. Available at www.chemsystems.com/reports/search/docs/ abstracts/0708S4_abs.pdf
64. Fantoni, L., and Simoneau, C. 2003. European Survey of Contamination of Homogenized Baby Food by Epoxidized Soybean Oil Migration from Plasticized PVC Gaskets. Food Additives and Contaminants, 20(11): 1087-1096.
65. European Commission Directorate – General Enterprise. 2000. Final Report: The Availability of Substitutes for Soft PVC Containing Phthalates in Certain Toys and Childcare Articles. Available at www.rpaltd.co.uk/ documents/phthalates_000.pdf
66. Stuer-Lauridsen, F., Mikkelsen, S., Havelund, S., Birkved M., and Hansen, L. P. 2001. COWI Consulting Engineers and Planners AS, Environmental Project No. 590: Environmental and Health

Assessment of Alternatives to Phthalates and to Flexible PVC. Available at http:// www2.mst.dk/udgiv/Publications/2001/87-7944-407-5/ pdf/87-7944-408-3.pdf
67. U.S. Consumer Product Safety Commission. (2010). Review of Exposure and Toxicity Data for Phthalate Substitutes: Di-isononyl-cyclohexane-1, 2-dicarboxylate (DINCH). Available at www.cpsc.gov/about/cpsia/ phthalsub.pdf
68. Carolina International Sales Co., Inc (CISCO). Material Safety Data Sheet (MSDS): Dioctyl Terephthalate. Available at www.ciscochem.com/msds/files/ Dioctyl_Terephthalate.pdf
69. Lanxess, Plastic Additives Technical Information: Mesamoll II. Available at http://techcenter.lanxess.com/ fcc/emea/en/products/datasheet/Mesamoll_II_(en).pdf?docId=8158992&gid=8158969&pid=1154
70. U.S. National Library of Medicine, Toxicology Data Network (TOXNET), Hazardous Substances Data Bank: Dioctyl Terephthalate. Available at http://toxnet.nlm.nih.gov/
71. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). (2007). Preliminary Report on the Safety of Medical Devices Containing DOP Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk. European Commission Health and Consumer Protection Directorate-General. Available at http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_008.pdf