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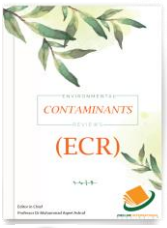

RESEARCH ARTICLE

LEACHING AND EXPOSURE OF PHTHALATES FROM MEDICAL DEVICES; HEALTH IMPACTS AND REGULATIONS

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ABSTRACT

Phthalates (PAEs) are widely used as plasticizers in medical devices to make polyvinyl chloride flexible and soft. However, PAEs can be leached out from plasticizers undesirably and can migrate within the material and end up with direct exposure to humans. Therefore, a number of studies have been conducted globally focusing on their leaching from medical devices like blood bags, infusion tubing, peritoneal dialysis bags and tubing, catheters etc. In current review an attempt is made to gather information related to leaching, exposure, health implication of PAEs along with the regulation used in different countries. Toxic health effects with the exposure of PAEs includes neurological effects, DNA damage, oxidative stress, asthma with negative impact on lungs, effects on reproductive system, liver impairment and gastrointestinal effects. In addition, leaching studies has shown the presence of DEHP about 31 – 34 % in peritoneal dialysis set like bags and tubing. DEHP leached out from medical apparatus depends upon temperature, storage time, amount of DEHP present in devices and shaking of device while in touched with medical solution. The exposure of plasticizers for pregnant hospitalised women and infants has also highlighted. In addition, PAEs alternates introduced in market are also discussed like Trioctyltrimellitate/tri-(2-ethylhexyl) trimellitate) along with various regulations regarding the use of PAEs in medical devices and other products.
was poor.

KEYWORDS

PAEs leaching, exposure, health implication Medical devices, PAEs alternatives, labeling issues

1. INTRODUCTION

Esters of phthalic acids (PAEs) are class of xenobiotic organic compounds which are extensively used for the formation of plastic goods and for making them more flexible. These are not chemically bound to plastics; hence they can easily leach out from it and get mix into surrounding environment [1,2]. 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) which contains an average 20–40% DEHP by mass [3,4]. PAEs are used to increase transparency, and durability of plastic materials since 1930s.

Each year the production of PAEs is 6 million tons; while in Europe, 1 million tons of PAEs are being manufactured annually [5,6]. Accordingly to low molecular weight, PAEs (low M.W) (ester side-chain lengths, one to four carbons) consist of dimethyl phthalate (DMP), diethyl phthalate (DEP), Dibutyl phthalate (DBP), and Diisobutyl Phthalate (DIBP), dipropyl phthalate (DPrP), and high-molecular-weight PAEs (high M.W.) (ester side-chain lengths, 5 or more carbons) containing di-2-ethylhexyl phthalate (DEHP), di-n- octyl phthalate (DOP), benzylbutyl phthalate (BzBP), and di-isononyl phthalate (DINP) (Figure-1). The most dominant PAEs are DEHP, DiDP and DiNP [7]. The most commonly used PAEs are, DMP, DEP, DBP, DEHP.

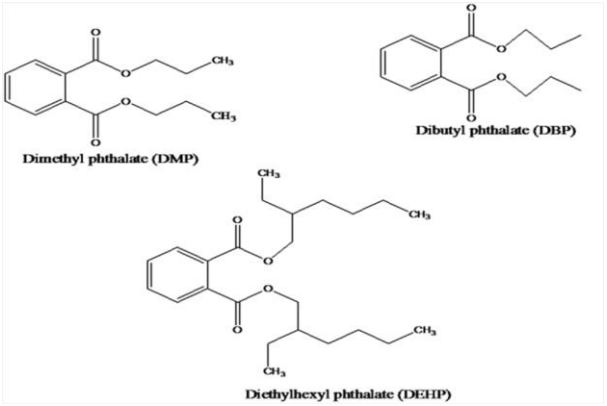

Figure 1: Structure of commonly used PAEs including DMP, DBP and DEHP

The consumers use eight different types of PAEs diesters generally, the (high M.W.) PAEs are generally found in wall covering, flooring and vinyl tubing; while (low M.W.) PAEs are commonly present in nail polish, personal care products and adhesives and printing ink [8]. In 1920s, PAEs were introduced first and were immediately substitute by odorous and volatile camphor. The production of PAEs was 1.8 to 4.3 million tons during 1970 and 2006 and during 2006 DINP had maximum production amount, followed by DEHP and DIDP, then BBP, DBP, DnOP, and DIBP [9]. In the ortho position, PAEs have a long alkyl side-chain likely for developmental and reproductive hazardous impacts in humans. The order of toxic potential of PAEs is DEHP>DBP>BBP in addition to DiNP, DnHP, and DiBP [10]. The DEHP is most common plasticizer that is not covalently attached to plastic material and can be released out from the product and can pollute the outer atmosphere. DEHP exposures from many sources through food appear to be the nearest to the bearable every day consumption of 2 mg/day in inhabitants [11]. However, when an individual goes through specific medical treatment, he may be exposed to greater quantity of DEHP by medical apparatus and plastics [12]. Inhalation, ingestion and dermal absorption are the different processes by which humans are exposed on daily bases [13,14]. Latex products, cellulose plastic and solvents for some dyes are widely formed by DBP and >70% of cosmetics and personal care products consist of DEHP [15]. PAEs are known as family of industrial compounds which possess wider range of industrial applications including personal care products and consumer. In addition, patients are highly exposed to these PAEs and DEHP containing medical devices [16].

When PAEs are released in the aquatic environment, they may be changed into other forms with this human health and aquatic ecosystem which are exposed to unknown risk [17]. Children having skin contact with surface and mouthing of fingers and other objects like plastic toys may lead to greater exposure of PAEs and intake of PAEs might be present in milk of cow, infant formula, breast milk or foodstuff packing [18]. As compare to adults, children are highly exposed to DEHP [19,20]. PAEs are known as the EDCs [21]. The developing fetus is exposed to EDs by breast feeding and placenta [22,23]. Due to these reasons, the French National Assembly (FNA) had banned parabens and PAEs (On 3 May 2011 Bill of Law followed by food and nutrition act (FNS). Moreover, prenatal phthalate exposure has been recommended to reduce child mental/motor development and raise internalizing behavior throughout the preschool time [24]. The exposure of PAEs cause the threat of allergic diseases which include eczema and asthma. This review is focused on the recent reports and evidences regarding the leaching of PAEs from medical devices, their toxicity, leaching, and exposure and health impacts as derived from relevant literature.

2. TOXIC EFFECTS OF PAES

In New York city 295 children were investigated and showed relationship between neonatal behavior and prenatal maternal urinary concentrations of PAEs metabolites and their result reported the relationship among neurological effect and prenatal PAEs exposure in animals or human beings [25]. In addition, a researcher studied infusion system containing the DEHP and the authors determined that by using DEHP – 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 [26]. The research work was carried out over the mice. The results showed that DEHP induced hepatic Tumorigensis through a peroxime proliferator – activated receptor a – in depended (PPARa) while DEHP caused the liver tumorigensis [27]. The authors recommended that DEHP induced which increased the oxidative stress and caused the inflammation or the expression of protooncogenes and resulted in the tumorigensis in PPARa – null mice.

2.1 Neurological effects

A research was conducted over the acute postnatal exposure to DEHP adversely impacts hippocampal development in the male rat by [28]. The researchers found that with exposure of (DEHP; 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 correspondingly in male rats and the same marker was found in the hippocampus of female rats in saline and DEHP treated animals. The studies of animals suggest that prenatal PAEs exposure is possible to enhance the risk of neurodevelopment impairment [29]. The study of elucidating the links between EDCs and neurodevelopment was carried out by Schug and the authors found that with the exposure of EDCs via PAES alter the brain function in children and disease susceptibility later in life [30].

2.2 DNA damage

The PAEs and their association between exposures of PAEs in environment and deoxyribos nucleic acid (DNA) damage in sperms related to humans by using the neutral comet assay. The author (Duty et al. 2003) showed that the first human records to express that urinary MEP at environmental levels are related to increased DNA damage in sperm. Along with this a researcher showed through his research over DNA damage in human sperm and the authors came to know that DEHP is linked with greater DNA damage in a group of men exposed through DEHP and another study was conducted by a researcher which showed that with the exposure of DEP the increase took place in DNA damage in sperm [31].

2.3 Oxidative stress

The cerebral neurotoxicity has risen by PAEs and DBP has been reported Recently by a researcher the cause of the neurological diseases and neurobehavioral changes [32]. The authors have determined the neurobehavioral changes in the brain of mouse caused by DBP may be mediated by oxidative damage and the co-administration of Mangiferin (MAG, 50 mg/kg/day) may save the brain against oxidative damage caused by exposure of DBP. Oxidative stress in the mouse brain exposes the relationship in between oxidative stress and behavior like anxiety is formed by DBP at greater doses of (25 or 125 mg/kg/day). The impact of intravenous lipid infusion on serum levels of malondialdehyde, which is creation of free radical-induced polyunsaturated fatty acid degradation, was studied in 7 infants and in group of children going under cyclic parenteral nutrition and receiving hyperalimentation via PVC tubing [33]. At the time of inflammation, the radicals of oxygen are the significant contributors to tissue damage and DEHP has exposed the enhance in oxidative stress; while MEHP increased the production of H_2O_2 in neutrophils [34].

2.4 Effect on lungs

The studies of DEHP effects on cell proliferation and tissues in lungs of infant rats carried out by [35]. In his studies, DEHP was given to female rats in the last days of pregnancy and the author analyzed at different periods of 2, 7 and 14 days postnatally encompassing the complete during alveolarization; while lung histology showed the swelling of air spaces and decrease of respiratory surface region and researched over the perinatal exposure of DEHP that leads delayed lung maturation and limited growth in newborn rats, the authors found that the maximum dose of DEHP (750 mg/kg/day) increased the lung tissue interstitial section ($P<0.001$) and decreased gas exchanges space [36]. A previous researcher reported his research through the risk of exposure to PAEs from PVC material in the enlargement of allergies, asthma, meta-analysis and systematic review [37]. The authors found that with exposure of PAEs from the PVC products cause asthma in young ones and epidemiologic studies in kids showed relations between indicators of PAEs exposure in the home and risk of allergies and asthma. Wheezing, asthma and rhinitis, in children could be related to larger quantity of DEHP and BBP in house dust [38,39].

2.5 Reproduction effects

While doing the research over the PAEs it was found that DEHP decreases the testicular weight and the production of sperms and contributes to the atrophy of seminiferous tubules which leads to infertility and damage liver, kidney, thyroid and spleen cancer in male rodents [40]. During the study of laboratory rats performed by a scholar, it was found that PAEs are responsible for the decreased production of estradiol which is sex hormone and is mainly responsible for the growth of reproductive organs in females and determined that with the exposure of PAEs lead to the disorders in the development of reproduction and in testicular dysgenesis in humans [41].

2.6 Effects over liver

PAES produced the different types of adverse effects which includes the liver tumors in mice and rats, along with this leydig cells and cells of

pancreas create tumors in rats was conducted by a researcher and another researcher carried out the studies over the Reexamination of the PPAR-α activation mode of action as a foundation for analyzing human cancer risks of atmospheric pollutant [42,43]. Conclusively, the authors came to know that DEHP generates liver tumors in rodents which depend upon PPAR-α activation and this is not related to human beings. Moreover, a researcher conducted study about the DEHP creates hepatic tumorigenesis by a peroxisome proliferator-activated receptor alpha-independent pathway and the authors determined through their two studies that liver tumors are produced by DEHP in mice and liver tumors may be produced by alternative mechanism.

2.7 Gastrointestinal effects

In 2009 the study carried out by a researcher in his article "the use of DEHP possessed by infusion systems raised the risk of cholestasis" in two to three-year periods. The author found that children who were fed through plasticized DEHP PVC infusion systems for total parental nutrition (TPN) raised cholestasis risk by a part of 5.6; while the use of free DEHP infusion systems for TPN is suggested particularly in infants.

3. LEACHING STUDIES

The leaching studies of adult patients undergoing peritoneal dialysis and parental nutrition and their result showed the presence of DEHP about 31 – 34 % in peritoneal dialysis set like bags and tubing. Solution for peritoneal dialysis was kept in the analyzed PVC bag, contained less quantity of 3.72μg dm^{-3} and infusion bottles composed of low-density polyethylene (LDEP) contained the low amount of DEHP than PVC bags. LDEP bottles used for packing physiological saline solution (0.9% NaCl) exposed greater quantity of DEHP than Ringer's solution prepared by LDEP. Concentration of DEHP in physiological saline and Ringer's solution was 17.30 and 5.83μgdm^3. Later on, leaching studies of PAEs were investigated by a researcher [44]. The authors showed the leached amount of PAEs like DEHP, DEHT, DINCH, TOTM utilized in medical tools of artificial nutrition and infusion process. The migration studies of PAEs were carried out under the temperature of 40°C with different intervals of 1 day, 3 days and 10 days. The maximum migration of PAEs enhanced with moment in time. Neonatal intensive care unit of Taiwan where have determined the leaching of PAEs and their metabolites from 32 premature neonates, 20 with very less birth weight (<1500 g) and 12 with birth weight of (<2500 g) [45]. The authors collected their urine samples and determined three metabolites of DEHP by using Tendam mass spectrometry, reversed phase high performance liquid chromatography and atmospheric pressure chemical ionization. They treated medium level of DEHP metabolites with an orogastric tube or nasogastric tube and endotracheal tube were considerably greater than those which were not treated with orogastric tube or nasogastric tube and endotracheal tube. Median level of DEHP was treated with intravenous injections which were less than 2-fold and higher than healthy that got intravenous injections ($p = 0.01$). Low birth neonates were found to have similar median level of PAEs metabolite. Along with this (Rose et al. 2012) have determined the leached quantity of DEHP from infusion sets, Mediplus TIVA, non-lipid and lipid infusates. Solutions were infused through TIVA sets at 12 $ml.h^{-1}$ for 6hours at 24°C, 32°C and 37°C and at 24 and 37°C TIVA sets were filled with two ml infusates, incubated and sealed. After dynamic and static contact PAEs was determined in every lipid infusates. A researcher has reported the leaching of PAEs from medical devices filled by medical solution during newborns, because of their little body mass and many medical devices associated to the DEHP exposure. The authors found that DEHP leached out from medical apparatus depends upon temperature, storage time, amount of DEHP present in devices and shaking of device while in touched with medical solution and degree of PVC degradation. A study has found that the amount of PAEs leached out from the 78 blood bags produced in Japan. DEHP and MEHP were determined directly by using LC – MS coupled with on – line extraction [46]. The highest amount about 0.7 mg/kg weight/time was leached from PVC bags as compared to other blood products. The leached DEHP from the PVC tubing by using polysorbate 80 (Tween 80) aqueous solution was carried out by a researcher. The authors found the released and increased amount of DEHP by increased temperature and velocity of circulation and the diffusion coefficients were found to be [D x 10^{-10} cm^2 $mint^{-1}$] at 5 and 40°C were 9.1 and 156.0 [47].

4. EXPOSURE STUDY

The exposure of plasticizers from pregnant hospitalized women and it was found that PAEs, Di (isononyl)-cyclohexane-1,2-dicarboxilic acid Tri-octyltrimellitate (TOTM) and Di-(isononyl) (DINP) which were dominant in the medical devices at a quantity of 29 to 36g per 100g of PVC. The women of "pathology group" were shown median number of PAEs from 2 medical devices possessing DINP and TOTM which were less than delivery and pathology group ($p < 0.05$). The pathology group exposed 3.4 h/day in a medical device having DINP and the medical device containing TOTM had exposure of 8.2 h/day, both were greater than the delivery group ($p < 0.01$) [48]. Along with this assessed the kinds and magnitudes of non-endocrine toxic risks to neonates related to medical device and DEHP exposures [49]. The authors found that daily intake of DEHP in infants can achieve 16 mg/kg per day that is the order of 4000 and 160,000 times maximum than desired to protect hepatic and reproductive toxicities. The non-endocrine toxicities of DEHP were found same in complications experienced by preterm neonates. Later on, a researcher quantified the DEHP from blood bags by using n – hexane and the extraction was performed by isolating 3 mycelial fungi as *Penicillium funiculosum*, *Fusarium subglutinans* and *Aspergillus parasiticus* from heavily plastics-contaminated soil and their growth took place under 28°C in basal salt medium [50]. In order to remove DEHP two stage cultivation strategies were adopted, in first growth stage 70% of DEHP present in blood bag was utilized in 14 days, by greater fungal biomass (~0.15–0.35 g/g BB; OD ~7 at 600 nm) and initial pH of (7.2) a sharp declined was (3.3). In second stage, remaining 99% DEHP was recovered from blood bags under the low pH. PAEs are exposed widely in environment as well as in humans and studies were conducted by a researcher and authors showed that due to exposure of PAEs the pathogenesis of allergic and asthma disorders raised [51]. The authors found the impact of PAEs in ensuing smooth muscle cells, cell – cell interaction, bronchial and airway epithelial cells which simulates the pathophysiology of airway remodeling in inflammatory and asthma air way disorders.

Table1: Leaching of PAEs from various medical devices in different countries

S.No.	Leaching Matrix	PAEs detected	Total	Country	Reference
1	Into pure platelet pheresis concentrate	DEHP	2090–10,670 μg/L	Austria	[52]
2	PVC bag	DEHP	1900 μg/L	Brazil	[53]
3	PVC disks	DEHP	1.91% in 3 weeks	Canada	[54]
4	Infusion and artificial nutrition	DEHP	31.1 mass %	France	[55]
5	Blood bags	DEHP	(33.5%, w/w)	India	[50]
6	Endotracheal tubes	DEHP	21%	Itlay	[23]
7	In whole blood (PVC blood bag)	DEHP	50,000–70,000 μg/L	Japan	[46]
8	Intravenous administration set	DEHP	9.1 D×10−10 (cm^2 /min)	Japan	[47]

9	Blood bags	DEHP	16.3µg/kg/day in men age 18-80 years	New york	[56]
10	Peritoneal dialysis set (bag and tubing	DEHP	3.72 µg dm^{-3}	Serbia	[57]
11	Endotracheal tube and Nasogastric tube	Sum of DEHP & its metabolites	2924.4 ng/mL	Taiwan	[45]
12	Diprivan and Propoven	DEHP	300-1600 µg/L	UK	[58]

There is a great impact of PAEs over humans due to their exposure, like, dibutyl phthalate (DBP), di – isononyl phthalate (DiNP), di – isodecyl phthalate (DIDP), butylbenzyl phthalate (BBP), DEHP and di – n – octyl phthalate (DOP) have been studied by a researcher.

These PAEs are used as plasticizers products formed by PVC such as toys, bags, plastic tubing gloves and plastics used for processing food and personal care products. PAEs are leached out from them and exposed through ingestion, inhalation and skin contact. Leaching of PAEs from different medical equipments which are reported in literature is shown in Table-1.

In July 2013 to December 2013, the project "Alternatives to PAEs in medical instruments" was carried out. This list was circulated in Europe to different manufacturing of alternatives, producers of various medical devices using under mentioned substituent of PAEs.

Alternative identified plasticizers along with chemical formula and full name are given in Table 2, while their structures are depicted in fig.2

Table 2: Chemical formula and full names of reported alternate plasticizer

S.NO.	Representation	Full name	Chemical formula
1	ATBC	Tributyl O-acetylcitrate	$C_{20}H_{34}O_8$
2	BTHC	Butyl trihexyl citrate	$C_{28}H_{50}O_8$
3	DEHT	Bis(2-ethylhexyl) terephthalate	$C_{24}H_{38}O_4$
4	DINA	Diisononyl adipate	$C_{24}H_{46}O_4$
5	DINCH	Diisononylcyclohexane dicarboxylate	$C_{26}H_{48}O_4$
6	TOTM/TEHTM	Trioctyltrimellitate/tri-(2-ethylhexyl)trimellitate)	$C_{33}H_{54}O_6/C_{24}H_{38}O_4$
7	DOA/DEHA	Bis(2-Ethylhexyl) Adipate	$C_{22}H_{42}O_4$

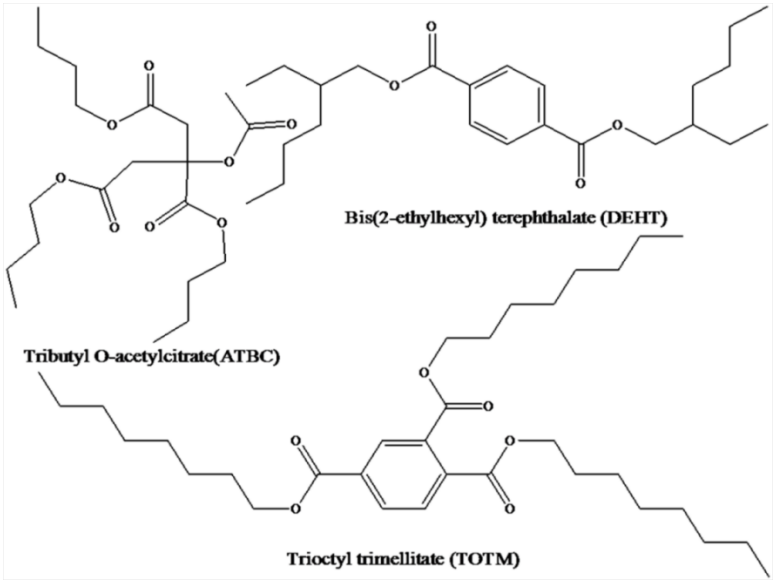

Figure 2: Structure of PAEs alternates, ATBC, DEHT and TOTM

There is a new guideline to use the alternative plasticizer of DEHP proposed by a researcher [59]. Various countries of the world (e.g., the United States, Germany, Switzerland, Austria) widely use Diisononyl cyclohexane dicarboxylate (DINCH) as a substitute of DEHP [60-63]. There are various alternative materials like silicones and polyolefines which do not require any plasticizers to be used. Currently different DEHP alternatives for the medical devices are being used for the safe side and the most important are DINCH, DEHT, adipates and citrates. In addition, other substitute of DEHP includes TOTM and TEHTM has been used in medical devices [64]. All the substitutes of DEHP are less toxic, particularly TOTM is claimed to be highly stable and has less migration rate from blood and other liquid. Currently available toxicological data has suggested that DPHP and DINCH have no effect over reproduction and endocrine system [65,66]. People are more exposed to DPHP and its high consumption has decreased the use of another high M.W PAEs. DINCH is non-aromatic plasticizer created by the addition of hydrogen DINP. It was commercialized in 2002 and its production was increased up to 200,000 in 2013. Bis(2-ethylhexyl) terephthalate (DEHT) and DEHP have more

toxicity as compared to DEHT and do not show any effect over production, genotoxicity, carcinogenicity and seem to be protective in the applications of infusion tubing stump [67-71]. Di(2-ethylhexyl) -1,2-cyclohexane dicarboxylate (DEHCH) was studied over SD rats for reproductive and developmental studies by a researcher [72]. Conclusively, it was reported that DEHCH posed a minimal effect over spleen. There was no indication of developmental, reproductive or toxicant effects in rats at reference dose of 0.3 mg/kg/day, as compared to the hazardous effect related to other plasticizer alternatives. The identification and quantification of 9 PAE's and 5 free plasticizer PAE's were done by a researcher using GC – MS. 61 medical devices were taken having one or more PVC material and among them 8 PAEs classified H360 (DiBP, DPP, DBP, BBP, DiPP, DEHP, DnPP, and DMEP), three PAEs were suggested not to be allowed in medical apparatus (DiNP, DnOP, and DiDP) and three other PAEs none regulated dicyclohexyl PAEs (DCHP), DMP and DEP may disturb the functions of hormone [73]. Five non-phthalate plasticizers (DINCH, DEHA, ATBC, TOTM and DEHT) are the substitute of DEHP in medical devices, were included in their research study. A previous researcher has done the collectively studies over the release of PAEs from the PVC tubing substances of heart-lung machine which is used for the cardiopulmonary bypass in children and the authors analyzed that leaching amount of DEHP plasticizer from PVC was comparatively higher than the TOTM and the degradation of TOTM was lower (by a factor of approx. [74]. 350). In a conclusion the TOTM proved to be an effective plasticizer in PVC tubing by having less migration time during medical procedure than DEHP. The exposure study was conducted by a scholar to analyze the PAEs like DINCH among the common population of Australian [75]. The authors collected the pooled urine sample from the different people of gender and age and the concentration was measured by solid phase extraction, tandem mass spectrometry and isotope dilution high performance liquid chromatography. Concentrations ranged from 2.4 to 71.9ng/ml for metabolites of DEHP, and from < 0.5 to 775ng/ml for total other metabolites, which was higher than the concentration of DINCH metabolites and their concentration was found to be very low. Currently a researcher showed the multiple paths of PAEs exposure by human and DINCH by skin absorption, respiration, and ingestion [76]. The author concluded that DINCH was found to be lower among the population having lower health-based limit values than other PAEs like DPHP, DEP, DMP, DiBP, DEHP, DIDP, DnBP, DINP and BBzP used from personal (hand wipes), indoor air, dietary (food) house dust and samples from a Norwegian cohort of 61 young ones and their households in the Oslo area. The common PVC substituents of DEHP are polypropylene (PP) polyethylene (PE) ethylvinylacetate (EVA) and thermoplastic elastomers like polyurethanes (PU) and fluoropolymers. Blood bags formed from EVA are having high flexibility toughness and sealing properties maximum resistance to outer influences [77]. PU and TPE both of the monomers can be either aromatic or aliphatic were better than PVC [78,79]. Fluoropolymer the last important group has explored that medical devices have good biocompatibility because of their hydrophilic surfaces. Such water loving materials decrease proteins adsorption and components of cell like leukocytes, fibroblasts, erythrocytes and platelets reduce blood clotting and decrease leaching of plasticizers [80]. It is clear that alternates did not possess similar toxicological nature as present in DEHP related to development and reproduction, but DOA is supposed to be similar in structure, metabolism and effects over the male reproductive system as DEHP. DOA has exposed indication for the activity of endocrine and effects over function of thyroid hormone. DINCH and DEHT are the successful alternates of DEHP with respect to EDCs and reproductive toxicity. It has been emphasized that this assessment is mainly based on the presence of data from the substances' REACH registration dossiers [81].

France has banned tubes containing DEHP in neonatology, maternity wards in hospitals and pediatrics in December 2012 and ban was regulated from July 2015. Besides, it was decided to stop using BBP and DBP in every medical device. In EU and current European commission has allowed PAEs in medical devices with labeling of DEHP, BBP, DIBP and DBP which are known as hazardous of carcinogenicity, mutagenic and reproduction. According to REACH (CMR substances Category 1a and 1b) and are used to control or remove medicine, body fluids or such substances from the body, or intended for pass and storage of these body fluids [82].

Increasing facts of health effects, these PAEs have been banned toys of children in the USA (CPSIA 2008), and EU 2005), Canada (HPA 2010). Before 10 years, DEHP has been forbidden to utilize in children's toys throughout the Western world [83]. It has been decided in Denmark, to introduce a ban of 4 PAEs DIBP, DBP, DEHP and BBP in utilizing substances for indoor use, and also for products with plasticized parts that may come into touch with mucous membranes and skin. The French National Assembly in May 2011 banned PAEs, alkylphenols and parabens by passing bill. PAEs use has been stopped in the EU for some years because of their risk of exposure which was raised by sucking or chewing the substances for more time Chronic Hazard Advisory [84]. In EU, limitations have been forced to ban on 5 particular PAEs, DEHP, BBP, DBP, DIDP and, DINP by Commission Directive 2007/19/EC.

The rising ease and use of alternative medical devices in various parts to increase alertness of health impacts caused by DEHP was raised by academic and advocacy groups like Sustainable Hospitals Project, Health Care Without Harm (HCWH) and the issuance of international health and policy notifications by Health Canada, EU and the united states food and drug administration (FDA) [85]. Europe and U.S has assessed the side effects of PAEs and efforts have taken to regulate such compounds. In EU regulations banned 6 PAEs in plastics which are exposed in many children and newborns. Before 2005, many states of U.S had attempted effectively to follow this regulation. National legislation put such types of limitations on PAEs in 2008 which were enacted in U.S. Table 3 describes the banned PAEs in different countries with distinctive periods.

Table 3: Different countries time line action against PAEs banning

S: No	Countries	Action	Year	References
1	Austria	Banned PAEs in toys	1998-1999	[86]
2	Belgium	Ceased soft PVC toys	1997	
3	Canada	Banned PAE in toys	2010	[87]
4	Denmark	Banned PAEs in toys and hand care articles	1999-2000	[86]
5	EU	Banned PAE in toys	2005	[88]
6	EU legislation	banned DEHP, DnBP and BBzP in toys and in childcare articles.	2005	[49]
7	France	DEHP containing tubes in neonatal, pediatric and maternity unit	2015	[40]
8	French national assembly	Banned PAEs	2011	
9	Finland	Government 5 PAEs in toys and childcare	1999	

10	Germany	Banned the use of all PAEs in teething rings	1999	[86-92]
11	Greece	Banned all PVC soft toys	1999	
12	Italy	37 Provinces passed resolutions opposing the use of soft PVC toys	1998	
13	Mexico	Stopped the import of soft PVC toys	1998	
14	Norway	Banned PAEs in toys	1999	[83]
15	Sweden	Banned PAEs in toys	1999	[88]
16	USA	Banned PAE in toys	2008	

5. CONCLUSION

Present review has indicated that medical devices are one of the major sources which have contributed to the leaching of PAEs such as DMP, DEP, DPrP, DBP, DEHP and DIBP. PAEs are leached out from them and exposed through ingestion, inhalation and skin contact. Studies with reference to infants have found that daily intake of DEHP in newborn can arrive at 16 mg/kg every day that is the order of 4000 and 160,000 times greater than preferred values to avoid hepatic and reproductive toxicities. Due to increasing awareness among general population the alternates like DEHT, DINA, DINCH and TOTM/TEHTM are being focused in many developed countries as successful substitutes. Hence, this is the time to keep the consumers aware by labeling over medical devices as free from plasticizers.

List of abbreviations

Full Name	Abbreviation
Phthalates	PAEs
Polyvinyl chloride	PVC
Dimethyl phthalate	DMP
Diethyl phthalate	DEP
Dipropyl phthalate	DPrP
Dibutyl phthalate	DBP
Di-2-ethylhexyl phthalate	DEHP
Benzylbutyl phthalate	BBP
Di-isononyl phthalate	DiNP
Di-n- octyl phthalate	DOP
Dicylohexyl phthalate	DCHP
Endocrine disruptor chemicals	EDCs
Butylbenzyl phthalate	BBP
Endocrine disruptor	EDCs
Trioctyltrimellitate/tri-(2-ethylhexyl) trimellitate)	TOTM/TEHTM
Deoxyribos nucleic acid	DNA
Low density polyethylene	LDEP
Di – isodecyl phthalate	DIDP
Di(2-ethylhexyl)-1,2-cyclohexane dicarboxylate	DEHCH
Ethylvinylacetate	EVA
Thermoplastic elastomers	TPEs
European Union	EU
Food and Drug Administration	FDA
Bis(2-ethylhexyl) terephthalate	DEHT
French National Assembly	FNA

DECLARATION

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and material

Not applicable.

COMPETING INTERESTS

All the authors declare that they have competing interest.

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AUTHORS' CONTRIBUTION

SAH prepared the first draft of the review article with the assistance of FNT. While JAB and HIA prepared literature comparison data with the help of MAS and MKT. SAH compiled all literature finally with FNT.

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REFERENCES

[1] Pradeep, S., Benjamin, S. 2012. Mycelial fungi completely remediate di (2-ethylhexyl) phthalate, the hazardous plasticizer in PVC blood storage bag. Journal of hazardous materials, 235, 69-77.

[2] 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.

[3] 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.

[4] 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.

[5] Jia, W., Chu, X., Ling, Y., Huang, J., Chang, J. 2014. Analysis of phthalates in milk and milk products by liquid chromatography coupled to quadrupole Orbitrap high-resolution mass spectrometry. Journal of Chromatography A, 1362, 110-118.

[6] Surhio, M.A., Talpur, F.N., Nizamani, S.M., Talpur, M.K., Amin, F., Khaskheli, A.A. 2017b. Effective Bioremediation of Endocrine-Disrupting Phthalate Esters, Mediated by Bacillus Strains. Water, Air, & Soil Pollution, 228(10), 386.

[7] Zhang, D., Liu, H., Liang, Y., Wang, C., Liang, H., Cai, H. 2009. Distribution of phthalate esters in the groundwater of Jianghan plain, Hubei, China. Frontiers of Earth Science in China, 3(1), 73.

[8] Council, N.R. 2009. Phthalates and cumulative risk assessment: the tasks ahead: National Academies Press.

[9] Hannon, P.R., Flaws, J.A. 2015. The effects of phthalates on the ovary. Frontiers in endocrinology, 6, 8.

[10] 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.

[11] 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.

[12] 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.

[13] Halden, R.U. 2010. Plastics and health risks. Annual review of public health, 31, 179-194.

[14] Heudorf, U., Mersch-Sundermann, V., Angerer, J. 2007. Phthalates: toxicology and exposure. International journal of hygiene and environmental health, 210(5), 623-634.

[15] Crinnion, W.J. 2010. Toxic effects of the easily avoidable phthalates and parabens. Alternative Medicine Review, 15(3).

[16] Koch, H.M., Bolt, H.M., Preuss, R., Angerer, J. 2005. New metabolites of di (2-ethylhexyl) phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Archives of toxicology, 79(7), 367-376.

[17] 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.

[18] Braun, J.M., Sathyanarayana, S., Hauser, R. 2013. Phthalate exposure and children's health. Current opinion in pediatrics, 25(2), 247.

[19] 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.

[20] 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.

[21] 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.

[22] 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.

[23] 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.

[24] Whyatt, R.M., Liu, X., Rauh, V.A., Calafat, A.M., Just, A.C., Hoepner, L. 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environmental health perspectives, 120(2), 290.

[25] 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.

[26] von Rettberg, H., Hannman, T., Subotic, U., Brade, J., Schaible, T., Waag, K.L. 2009. Use of di (2-ethylhexyl) phthalate–containing infusion systems increases the risk for cholestasis. Pediatrics, 124(2), 710-716.

[27] Ito, Y., Yamanoshita, O., Asaeda, N., Tagawa, Y., Lee, C.H., Aoyama, T. 2007. Di (2-ethylhexyl) phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. Journal of Occupational Health, 49(3), 172-182.

[28] Smith, C., Macdonald, A., Holahan, M. 2011. Acute postnatal exposure to di (2-ethylhexyl) phthalate adversely impacts hippocampal development in the male rat. Neuroscience, 193, 100-108.

[29] 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.

[30] 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.

[31] 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.

[32] 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.

[33] 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.

[34] 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.

[35] Rosicarelli, B., Stefanini, S. 2009. DEHP effects on histology and cell proliferation in lung of newborn rats. Histochemistry and cell biology, 131(4), 491-500.

[36] 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.

[37] 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 health perspectives, 116(7), 845.

[38] Bornehag, C., Nanberg, E. 2010. Phthalate exposure and asthma in children. International journal of andrology, 33(2), 333-345.

[39] 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.

[40] 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.

[41] Eveillard, A., Mselli-Lakhal, L., Mogha, A., Lasserre, F., Polizzi, A., Pascussi, J.-M., et al. (2009). Di-(2-ethylhexyl)-phthalate (DEHP) activates the constitutive androstane receptor (CAR): a novel signalling pathway sensitive to phthalates. Biochemical pharmacology, 77(11), 1735-1746.

[42] Barr, D.B., Breysse, P.N., Chapin, R., Marcus, M. 2006. NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of di (2-ethylhexyl) phthalate. Reproductive toxicology, 22, 291-399.

[43] 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.

[44] 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 the extraction procedures, a pre-migration test step. Analytical and bioanalytical chemistry, 407(6), 1651-1659.

[45] Su, P.H., Chang, Y.Z., Chang, H.P., Wang, S.L., Haung, H.I., Huang, P.C. 2012. Exposure to di (2-ethylhexyl) phthalate in premature neonates in a neonatal intensive care unit in Taiwan. Pediatric Critical Care Medicine, 13(6), 671-677.

[46] 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.

[47] 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.

[48] Marie, C., Hamlaoui, S., Bernard, L., Bourdeaux, D., Sautou, V., Lémery, D. 2017. Exposure of hospitalised pregnant women to plasticizers contained in medical devices. BMC women's health, 17(1), 45.

[49] Mallow, E., Fox, M. 2014. Phthalates and critically ill neonates: device-related exposures and non-endocrine toxic risks. Journal of Perinatology, 34(12), 892.

[50] Pradeep, S., Faseela, P., Josh, M.S., Balachandran, S., Devi, R.S., Benjamin, S. 2013. Fungal biodegradation of phthalate plasticizer in situ. Biodegradation, 24(2), 257-267.

[51] Tsai, M.J., Kuo, P.L., Ko, Y.C. 2012. The association between phthalate exposure and asthma. The Kaohsiung journal of medical sciences, 28(7), S28-S36.

[52] Buchta, C., Bittner, C., Höcker, P., Macher, M., Schmid, R., Seger, C. 2003. Donor exposure to the plasticizer di (2-ethylhexyl) phthalate during plateletpheresis. Transfusion, 43(8), 1115-1120.

[53] Veiga, M., Bohrer, D., Nascimento, P.C., Ramirez, A.G., Carvalho, L.M., Binotto, R. 2012. Migration of phthalate-based plasticizers from PVC and non-PVC containers and medical devices. Journal of the Brazilian Chemical Society, 23(1), 72-77.

[54] Kastner, J., Cooper, D.G., Marić, M., Dodd, P., Yargeau, V. 2012. Aqueous leaching of di-2-ethylhexyl phthalate and "green" plasticizers from poly (vinyl chloride). Science of the total environment, 432, 357-364.

[55] Bernard, L., Cueff, R., Breysse, C., Décaudin, B., Sautou, V., Group, A.S. 2015. Migrability of PVC plasticizers from medical devices into a simulant of infused solutions. International journal of pharmaceutics, 485(1-2), 341-347.

[56] Shaz, B.H., Grima, K., Hillyer, C.D. 2011. 2-(Diethylhexyl) phthalate in blood bags: is this a public health issue? Transfusion, 51(11), 2510-2517.

[57] Kostić, I.S., Anđelković, T.D., Anđelković, D.H., Cvetković, T.P., Pavlović, D.D. 2016. Determination of di (2-ethylhexyl) phthalate in plastic medical devices. Hemijska industrija, 70(2), 159-164.

[58] Rose, R., Priston, M., Rigby-Jones, A., Sneyd, J. 2012. The effect of temperature on di (2-ethylhexyl) phthalate leaching from PVC infusion sets exposed to lipid emulsions. Anaesthesia, 67(5), 514-520.

[59] Chiellini, F., Ferri, M., Morelli, A., Dipaola, L., Latini, G. 2013. Perspectives on alternatives to phthalate plasticized poly (vinyl chloride) in medical devices applications. Progress in Polymer Science, 38(7), 1067-1088.

[60] Bui, T.T., Giovanoulis, G., Cousins, A.P., Magnér, J., Cousins, I.T., de Wit, C.A. 2016. Human exposure, hazard and risk of alternative plasticizers to phthalate esters. Science of the Total Environment, 541, 451-467.

[61] Lessmann, F., Schütze, A., Weiss, T., Langsch, A., Otter, R., Brüning, T. 2016. Metabolism and urinary excretion kinetics of di (2-ethylhexyl) terephthalate (DEHTP) in three male volunteers after oral dosage. Archives of toxicology, 90(7), 1659-1667.

[62] Silva, M.J., Jia, T., Samandar, E., Preau Jr, J.L., Calafat, A.M. 2013. Environmental exposure to the plasticizer 1, 2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) in US adults (2000-2012). Environmental research, 126, 159-163.

[63] Silva, M.J., Wong, L.Y., Samandar, E., Preau, J.L., Calafat, A.M., Ye, X. 2017. Exposure to di-2-ethylhexyl terephthalate in a convenience sample of US adults from 2000 to 2016. Archives of toxicology, 91(10), 3287-3291.

[64] Van Vliet, E., Reitano, E., Chhabra, J., Bergen, G., Whyatt, R. 2011. A review of alternatives to di (2-ethylhexyl) phthalate-containing medical

devices in the neonatal intensive care unit. Journal of Perinatology, 31(8), 551.

[65] Bhat, V.S., Durham, J.L., Ball, G.L., English, J.C. 2014. Derivation of an oral reference dose (RfD) for the nonphthalate alternative plasticizer 1, 2-cyclohexane dicarboxylic acid, di-isononyl ester (DINCH). Journal of Toxicology and Environmental Health, Part B, 17(2), 63-94.

[66] Furr, J.R., Lambright, C.S., Wilson, V.S., Foster, P.M., Gray Jr, L.E. 2014. A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicological sciences, 140(2), 403-424.

[67] Testai, E. 2016. The safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update). Regulatory toxicology and pharmacology: RTP, 76, 209.

[68] Faber, W. D., Deyo, J.A., Stump, D.G., Ruble, K. 2007. Two-generation reproduction study of di-2-ethylhexyl terephthalate in Crl: CD rats. Birth Defects Research Part B: Developmental and Reproductive Toxicology, 80(2), 69-81.

[69] Barber, E., Fox, J., Giordano, C. 1994. Hydrolysis, absorption and metabolism of di (2-ethylhexyl) terephthalate in the rat. Xenobiotica, 24(5), 441-450.

[70] Deyo, J.A. 2008. Carcinogenicity and chronic toxicity of di-2-ethylhexyl terephthalate (DEHT) following a 2-year dietary exposure in Fischer 344 rats. Food and chemical toxicology, 46(3), 990-1005.

[71] Wirnitzer, U., Rickenbacher, U., Katerkamp, A., Schachtrupp, A. 2011. Systemic toxicity of di-2-ethylhexyl terephthalate (DEHT) in rodents following four weeks of intravenous exposure. Toxicology letters, 205(1), 8-14.

[72] Hughes, B.J., Cox, K., Bhat, V. 2018. Derivation of an oral reference dose (RfD) for di 2-ethylhexyl cyclohexan-1, 4-dicarboxylate (DEHCH), an alternative to phthalate plasticizers. Regulatory Toxicology and Pharmacology, 92, 128-137.

[73] Gimeno, P., Thomas, S., Bousquet, C., Maggio, A.F., Civade, C., Brenier, C. 2014. Identification and quantification of 14 phthalates and 5 non-phthalate plasticizers in PVC medical devices by GC–MS. Journal of Chromatography B, 949, 99-108.

[74] Eckert, E., Münch, F., Göen, T., Purbojo, A., Müller, J., Cesnjevar, R. 2016. Comparative study on the migration of di-2-ethylhexyl phthalate (DEHP) and tri-2-ethylhexyl trimellitate (TOTM) into blood from PVC tubing material of a heart-lung machine. Chemosphere, 145, 10-16.

[75] Ramos, M.G., Heffernan, A., Toms, L., Calafat, A., Ye, X., Hobson, P. 2016. Concentrations of phthalates and DINCH metabolites in pooled urine from Queensland, Australia. Environment international, 88, 179-186.

[76] Giovanoulis, G., Bui, T., Xu, F., Papadopoulou, E., Padilla-Sanchez, J.A., Covaci, A. 2018. Multi-pathway human exposure assessment of phthalate esters and DINCH. Environment international, 112, 115-126.

[77] Simmchen, J., Ventura, R., Segura, J. 2012. Progress in the removal of di-[2-ethylhexyl]-phthalate as plasticizer in blood bags. Transfusion medicine reviews, 26(1), 27-37.

[78] Kelch, R. 2001. A new family of HF-weldable polyolefin films. Medical Device And Diagnostic Industry, 23(1), 82-98.

[79] Shah, T. 2002. Polyurethane thin-film welding for medical device applications. Medical Device and Diagnostic Industry, 24(9), 62-69.

[80] Rahman, M., Brazel, C.S. 2004. The plasticizer market: an assessment of traditional plasticizers and research trends to meet new challenges. Progress in Polymer Science, 29(12), 1223-1248.

[81] Danish, E. 2014. Alternative to classified phthalates in medical devices. Environmental Project No. 155, file:///C:/Users/Shoaib/Desktop/Alternatives%20to%20classified%20phthalates%20in%20medical%20devices.pdf.

[82] Health, C. 2013. Hazardous chemicals in medical devices: Phthalates [Web data]. https://noharm-europe.org/sites/default/files/documents-files/2103/2013-05-02_HCWH%20Europe%20Phthalate%20Factsheet.pdf.

[83] Erythropel, H.C., Maric, M., Nicell, J.A., Leask, R.L., Yargeau, V. 2014. Leaching of the plasticizer di (2-ethylhexyl) phthalate (DEHP) from plastic containers and the question of human exposure. Applied microbiology and biotechnology, 98(24), 9967-9981.

[84] Panel, C.H.A. 1985. Report to the US Consumer Product Safety Commission on Di (2-Ethylhexyl) Phtalate.

[85] Harris, N., Pisa, L., Talioaga, S., Vezeau, T. 2009. Hospitals going green: a holistic view of the issue and the critical role of the nurse leader. Holistic Nursing Practice, 23(2), 101-111.

[86] Di Gangi, J. 1999. Phthalates in PVC medical products from 12 countries. Greenpeace, Washington, DC.

[87] Flaherty, E. 2008. Safety first: the consumer product safety improvement act of 2008. Loy. Consumer L. Rev., 21, 372.

[88] Fontelles, J., Clarke, C. 2005. Directive 2005/84/EC of the European Parliament and of the Council of 14 December 2005 amending for the 22nd time Council Directive 76/69/EEC on the approximation of the laws, regulations and administrative provisions of the Men Der States relating to restrictions on the marketing and use of certain dangerous substances and preparations (phthalates in toys and childcare articles). Official Journal of the European Union, 48, 40-43.

[89] Hauser, R. 2008. Urinary phthalate metabolites and semen quality: a review of a potential biomarker of susceptibility. International journal of andrology, 31(2), 112-117.

[90] Duty, S.M., Singh, N.P., Silva, M.J., Barr, D.B., Brock, J.W., Ryan, L. 2003. The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. Environmental health perspectives, 111(9), 1164.

[91] Farahani, H., Ganjali, M.R., Dinarvand, R., Norouzi, P. 2008. Screening method for phthalate esters in water using liquid-phase microextraction based on the solidification of a floating organic microdrop combined with gas chromatography–mass spectrometry. Talanta, 76(4), 718-723.

[92] Tsumura, Y., Ishimitsu, S., Kaihara, A., Yoshii, K., Tonogai, Y. 2002. Phthalates, adipates, citrate and some of the other plasticizers detected in Japanese retail foods: a survey. Journal of health science, 48(6), 493-502.