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Medical devices as a source of phthalate exposure: a review of current knowledge and alternative solutions

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Phthalates are a group of phthalic acid esters used as plasticisers in a large number of products to improve their flexibility, softness, and extensibility. Their wide use in medical devices, however, raises a lot of concern, as they can enter the organism and have toxic effects on human liver, thyroid, kidneys, lungs, reproductive, endocrine, nervous, and respiratory system and are associated with asthma, obesity, autism, and diabetes. The aim of this review is to summarise current knowledge about phthalate migration from medical devices during different medical procedures and possible impact on patient health. It also looks at alternative plasticisers with supposedly lower migration rates and safer profile. Not enough is known about which and how many phthalates make part of medical devices or about the health impacts of alternative plasticisers or their migration rates.

KEY WORDS: plasticisers; human exposure; regulation; reproductive system disorders; toxicology

List of phthalate abbreviations

BBP – 2-O-benzyl 1-O-butyl benzene-1,2-dicarboxylate ($C_{19}H_{20}O_4$)
DBP – dibutyl benzene-1,2-dicarboxylate ($C_{16}H_{22}O_4$)
DBzP – dibenzyl benzene-1,2-dicarboxylate ($C_{22}H_{18}O_4$)
DEP – diethyl benzene-1,2-dicarboxylate ($C_{12}H_{14}O_4$)
DEHP – bis(2-ethylhexyl) benzene-1,2-dicarboxylate ($C_{24}H_{38}O_4$)
DIBP – bis(2-methylpropyl) benzene-1,2-dicarboxylate ($C_{16}H_{22}O_4$)
DIDP – bis(8-methylnonyl) benzene-1,2-dicarboxylate ($C_{28}H_{46}O_4$)
DINP – bis(7-methyloctyl) benzene-1,2-dicarboxylate ($C_{26}H_{42}O_4$)
DPHP – bis(2-propylheptyl) benzene-1,2-dicarboxylate ($C_{28}H_{46}O_4$)
DiUP – bis(8-methylnonyl) benzene-1,2-dicarboxylate ($C_{28}H_{46}O_4$)
DTDP – (2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl) oxolan-2-yl]methyl phosphono hydrogen phosphate ($C_{10}H_{16}N_2O_{11}P_2$)
DiPeP – bis(3-methylbutyl) benzene-1,2-dicarboxylate ($C_{18}H_{26}O_4$)
DMP – dimethyl benzene-1,2-dicarboxylate ($C_{10}H_{10}O_4$)
MBP – 2-butoxycarbonylbenzoic acid ($C_{12}H_{14}O_4$)
MnBP – 2-butoxycarbonylbenzoic acid ($C_{12}H_{14}O_4$)
MBzP – 2-phenylmethoxycarbonylbenzoic acid ($C_{15}H_{12}O_4$)
MCiOP – 2-(8-carboxyoctan-2-yloxycarbonyl)benzoic acid ($C_{17}H_{22}O_6$)
MCPP – 2-(3-carboxypropoxycarbonyl)benzoic acid ($C_{12}H_{12}O_6$)
MECPP – 2-(5-carboxy-2-ethylpentoxy)carbonylbenzoic acid ($C_{16}H_{20}O_6$)
MEHHP – 2-(2-ethyl-5-hydroxyhexoxy)carbonylbenzoic acid ($C_{16}H_{22}O_5$)
MEHP – 2-(2-ethylhexoxycarbonyl)benzoate ($C_{16}H_{21}O_4^-$)
MEOHP – 2-(2-ethyl-5-oxohexoxy)carbonylbenzoic acid ($C_{16}H_{20}O_5$)
MEP – 2-ethoxycarbonylbenzoic acid ($C_{10}H_{10}O_4$)
MMP – 2,3,4,5-tetradeuterio-6-methoxycarbonylbenzoic acid ($C_9H_8O_4$)

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Phthalates are phthalic acid esters used as plasticisers to improve the flexibility, softness, durability, and extensibility of a great variety of products (1–4), including many medical devices, such as intravenous (IV) solution, blood, feed, and peritoneal dialysis bags and infusion, transfusion, nasogastric, and umbilical artery tubes and catheters (5). Their use has revolutionised patient clinical care but has also raised concern over their noncovalent binding to materials, because of which they readily migrate into patient body, yet the direct effects on human health are still not clear (1–3). Exposure has been associated with reproductive, endocrine, nervous, and respiratory system disorders, asthma, obesity, autism, diabetes, and liver, thyroid, kidney, and lung toxicity (3).

The new European regulations on medical devices (6) and *in vitro* diagnostic medical devices (7) of 2021 and 2022, respectively, brought more stringent rules on the design and manufacturing of medical devices to reduce any possible risks from substances and particles that can leach or be released from these devices. The intent of this review was to take a look at recent literature about the presence of phthalates and their substitutes in medical devices and their impact on patient or user health.

Our literature search focused on studies indexed in PubMed and published in the last six years covering phthalates in medical devices, their observed and potential health effects, use of alternative plasticisers in medical devices, and their safety profiles.

PHTHALATE STRUCTURE AND PROPERTIES

Phthalates are the esters of 1,2-benzenedicarboxylic acid (o-phthalic acid) consisting of one benzene ring and two ester

functional groups connected with two consecutive carbons on the ring (8, 9). They are produced by a reaction between phthalic anhydride and alcohols ranging from methanol and ethanol to tridecanol. These alcohols are the bases of linear or branched hydrocarbon chains which define their properties. At a room temperature, they are almost colourless and odourless oil-based lipophilic liquids with a low melting point and relatively high boiling point, which makes them very useful as plasticiser in the polymer industry. Linear phthalates provide superior flexibility at low temperatures and lower volatility (8).

Depending on their carbon chain length, phthalates are classified as low molecular weight (LMW) with 3–6 carbon atoms in their side chain or high molecular weight (HMW) with 7–13 carbon atoms in the side chain. The most common in the LMW group are dibutyl benzene-1,2-dicarboxylate (DBP), bis(2-methylpropyl) benzene-1,2-dicarboxylate (DiBP), 2-O-benzyl 1-O-butyl benzene-1,2-dicarboxylate (BBP), and bis(2-ethylhexyl) benzene-1,2-dicarboxylate (DEHP). The HMW group includes bis(8-methylnonyl) benzene-1,2-dicarboxylate (DiDP), bis(7-methyloctyl) benzene-1,2-dicarboxylate (DiNP), bis(2-propylheptyl) benzene-1,2-dicarboxylate (DPHP), bis(8-methylnonyl) benzene-1,2-dicarboxylate (DiUP), and (2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphono hydrogen phosphate (DTDP), which are mostly used in industry and make 80 % of phthalate use in Europe. We shall, however, focus on LMW phthalates used in medical devices or for enteric coating and on the third group of phthalates with one or two carbon atoms in the side chain, namely dimethyl benzene-1,2-dicarboxylate (DMP) and diethyl benzene-1,2-dicarboxylate (DEP), which are used as solvents and fixatives in fragrances, additives in cosmetics, medical devices, and household and personal care products (8, 9). The amount of phthalates used in a certain product can reach up to 60 %, depending on the type and purpose (8). Annual phthalate consumption is more than one million tonnes in Western Europe and over three million tonnes around the world (10).

When used as plasticisers, phthalates bind to polymers non-covalently, which means that their bounds are temporary. Under certain conditions they tend to migrate from a material to the environment and – what is of particular concern – to patients during clinical treatment (1, 9–13). Patients can be exposed to phthalates through ingestion, inhalation, dermal absorption, and other parenteral routes (12). Studies have shown that phthalate migration depends on a number of factors, including flow rate, temperature, pH, contact time, and type of interaction between plasticisers and simulants (9, 11, 12, 14).

When phthalates enter the human body, their half-lives range from hours to several days before they are excreted in urine, sweat, or faeces (3, 9, 12). Parent compounds or their metabolites spread into the circulatory system, breast milk, amniotic fluid, semen, saliva, and adipose tissue. Phthalate metabolism usually includes two stages: hydrolysis and oxidation first to form hydrolytic monoesters and then conjugation to produce a number of hydrophilic glucuronide conjugates (3, 9). The higher the phthalate molecular weight, the lower its 24-hour excretion rate (9). Adults excrete phthalates conjugated to glucuronic acid via urine, but the conjugation pathway in infants is immature, especially in the premature ones, and their glomerular filtration rate is low (15).

TOXICITY

Depending on the stage of development and sex, phthalates will affect different systems in a different way and not all phthalates will cause adverse effects in both sexes (9).

Endocrine and reproductive toxicity

Having a chemical structure similar to naturally occurring steroid hormones in the human body, phthalates interact with endogenous receptors in organ systems and act as "endocrine disruptors". By mimicking or partly mimicking hormones such as oestrogens and androgens, phthalates can overstimulate, bind to, or block receptors and alter normal signalling pathways in hormone-responsive tissues (5, 9, 12, 16). Animal studies show a 50 % drop in aldosterone and testosterone, reduced steroidogenesis, histopathological changes in the thyroid of mice and rats (5), multigenerational and transgenerational adverse effects on ovarian function in mice due to DEHP exposure (17, 18), failed spermatogenesis, and even necrosis in some seminiferous tubules due to DBP exposure in adult rats (19). Carbone et al. (20) suggest that chronic postnatal exposure to DEHP disrupts neuroendocrine regulation of the testicular axis and promotes anxiety-like behaviour in male rats, but also consider the potential of gamma-aminobutyric acid (GABA) to suppress these effects of DEHP.

DEHP and its metabolites have high binding affinity for progesterone receptors sufficient to disrupt normal signalling (21). Phthalates also disrupt the function of Leydig and Sertoli cells in spermatogenesis and steroidogenesis, and their structural and metabolic support for developing germ cells. Males can develop the "testicular dysgenesis syndrome" followed by cryptorchidism hypospadias, reduced anogenital distance (AGD), altered seminal parameters, infertility, and testicular cancer (5, 8, 9, 22). DEHP has also been reported to affect male fertility by altering the sperm capacitation, impairing acrosome reaction, and increasing ROS production in a murine model (8, 23). Exposure of male rats to bis(3-methylbutyl) benzene-1,2-dicarboxylate (DiPeP) *in utero* and through milk can eventually affect their drive to search for or interact with females and their copulatory behaviour (24). Speaking of maternal milk, several studies have reported DEHP in it (5, 8, 16).

In females, exposure to phthalates is associated with follicular atresia, endometriosis, infertility, disorders in pubertal development, increased birth loss, and reduced yield of oocytes (25, 26).

Speaking about the association between phthalates and endometriosis, numerous studies have pointed to a mechanism of action that involves oxidative stress, inflammatory enzymes, and

hormone receptors (5, 26). One study linked endometriosis in women of reproductive age with DEHP exposure (5), and another with 2-butoxycarbonylbenzoic acid (MnBP), which, reportedly, affects gene expression and inhibin-B production, and lowers mitochondrial membrane potential in human granulosa cells and the expression of anti-Mullerian hormone (4). One study of DBP exposure *in utero* in mice showed disrupted DNA methyltransferase activity, which is indicative of epigenetic changes in the uterus (27), and many other studies associate phthalates with delayed foetal development, which manifests itself as low birth weight and rate of weight gain, preterm birth, and abnormal body parameters (including shorter AGD) in a newborn (9). 2-(5-carboxy-2-ethylpentoxy)carbonylbenzoic acid (MECPP) in amniotic fluid is associated with changes in foetal testosterone and insulin-like factor 3 levels and 2-(8-carboxyoctan-2-yloxycarbonyl)benzoic acid (MCiOP) with cryptorchidism and hypospadias (28).

Phthalates also seem to speed up puberty in girls and delay it in boys (29, 30).

They also increase the risk of thyroid endocrine system disruption. One study (5) showed that DEHP can reduce thyroxine (T4) levels in adult men and affect hepatic enzymes which have disrupting effects on the thyroid function. Other studies (31, 32) associated DEHP and its metabolites with the onset of type 2 diabetes, 2-butoxycarbonylbenzoic acid (MBP) with poor insulin secretion, and 2-ethoxycarbonylbenzoic acid (MEP) and 2,3,4,5-tetradeuterio-6-methoxycarbonylbenzoic acid (MMP) with insulin resistance.

Metabolic toxicity

An *in vitro* study with human Simpson-Golabi-Behmel syndrome (SGBS) derived adipocytes exposed to DEHP showed increased secretion of pro-inflammatory interleukin 8 (IL8) and monocyte chemoattractant protein 1 (MCP1) and significant accumulation of intracellular lipid droplets in macrophages (33).

Several epidemiological studies in elderly population showed increased insulin resistance after exposure to DEHP (31), including age and sex-dependent obesogenic activity of its metabolites (MEP, MEHP, MBzP, MEHHP, and MEOHP) (34, 35). In Chinese school children, exposure to MEHP was associated with higher BMI and waist circumference as markers of obesity (5). The link between obesity and MEHP was also found in healthy individuals of normal weight (36, 37). An association was also reported between higher MnBP and the prevalence of metabolic syndrome and dyslipidaemia in male adolescents (38). The same effect was reported for MEHP in obese and healthy adults (39), and MEHP has been associated with adipogenesis (40).

In mice, DEHP and MEHP have been reported to promote adipogenesis and even suppress osteogenesis (41).

Phthalate metabolism is widely known, but the association between metabolic processes and endocrine effects remains unclear. Some studies indicate that phthalate diesters are more toxic than monoesters (42), while others suggests diester or glucuronidated metabolic forms are non-toxic (43) Tian et al. (44), for example, report that the anti-androgenic effect of diester DBP is reversed into androgenic effect as it becomes hydrolysed into its monoester MBP and that diesters DBzP and DEHP have lower anti-androgenic potential than DBP, yet tend to downregulate androgens in Leydig cells. All these findings call for a deeper investigation into the association between hydrolytic processes and phthalate toxicity.

Two studies of how phthalates affect drug-metabolising uridine 5'-diphospho-glucuronosyltransferases (UGTs) (45, 46) confirmed limited inhibition of some recombinant human UGTs and possible interference with the metabolism of various endogenous and xenobiotic substances. Since UGT isoforms have a key role in metabolism of xenobiotics, this interference should be taken into account for patients exposed to phthalates.

Pulmonary toxicity

Knowledge about the pulmonary toxicity of phthalates is limited to animal studies with DEHP. A study in DEHP-treated rats (47) showed alveoli of varying shapes and sizes, some obliterated and others patented, but all with a thickened wall, infiltrated with inflammatory cells, and high type-II pneumocyte count and collagen deposition. Pathological changes improved after exposure was stopped, but the lung tissue did not recover completely. Another study in DEHP-exposed newborn rats (48) showed arrested lung alveolarisation and bronchopulmonary dysplasia when the rats were also exposed to hyperoxia.

Renal toxicity

Limited data on DEHP exposure in mice and rats point to an association with nephropathy and progression of the chronic kidney disease (CKD) (49–51). One animal study (52) has shown that DEHP, but not its metabolite MEHP, induced epithelial-mesenchymal transition (EMT) and renal fibrosis in renal tubular cells, and that these effects were associated with the downregulation of peroxisome proliferator-activated receptors (PPARs).

As for human data, impaired renal function has been associated with exposure to DEHP in adults (29, 53) and exposure to MEP, MBzP, and MOP in children (54). Dialysis patients seem to retain from 3.6 to 59.6 mg of DEHP per treatment, and long-term dialysis may lead to polycystic kidney disease (PKD) (55).

Hepatotoxicity

Current knowledge is limited to animal studies alone, which provide some understanding of phthalate liver toxicity. In rats and mice, phthalates in the doses of 50–1000 mg/kg a day showed the potential to cause liver tumours (56, 57). A characteristic response to DEHP exposure in the liver of rodents is higher fatty acid metabolism, hepatomegaly, lower glycogen storage, periportal accumulation of fat, and accumulation of lipofuscin granules (3,

5). DBP has been reported to damage liver tissue through oxidative stress and altered transaminase activity (58).

Based on animal findings, Praveena et al. (3) suggest that chronic exposure to phthalates in humans may lead to liver dysfunction as they inhibit detoxifying liver enzymes. An *in vitro* study by Gaitantzi et al. (59), which included human liver cells, supports this assumption, as it shows that DEHP in clinically relevant concentrations alters the expression and activity of drug detoxifying liver enzymes and might contribute to the development of cholestasis and fibrosis.

Cardiovascular toxicity

One study of rat hearts (1) points to metabolic remodelling and lower conduction velocity of cardiomyocytes, asynchronous cell beating caused by DEHP primary metabolite MEHP. Another study, in turn, showed negative chronotropic and inotropic effects of DEHP on human stem cell-derived cardiomyocytes (5).

Azevedo et al. (60) suggest that DEHP relaxes the human umbilical artery contracted by different agents when exposure is short-term. Long-term exposure with more than 10 nmol/L of DEHP, however, downregulates the expression of $5HT_{2A}$ receptors and annuls the relaxant effect of short-term exposure. Long-term exposure to low concentrations increases contraction.

Neurotoxicity

DEHP that crosses the placental barrier and enters foetal circulation can impair normal brain development and birth defects (61).

In animal studies, DEHP exposure (1500 mg/kg) *in utero* was reported to disturb lipid metabolism in foetal rat brain, which caused brain growth anomalies (62). Postnatal rat exposure affected the development of the hippocampus in males and decreased dendritic spine density (63). Perinatal exposure has also been associated with anxiety and depression-like behaviour in mice, whereas exposure to low concentrations of DEHP (50 and 200 mg/kg a day) *in utero* or through milk can impair spatial learning and memory (64, 65).

In humans, one major study of prenatal exposure to MBP (66) reported significant association with lower verbal comprehension and visual space indices in Chinese preschoolers and pointed to phthalate exposure in the first trimester as critical for cognitive development in children. Various markers of phthalate exposure across the gestation stage have been associated with lower frequency and higher amplitude of non-nutritive sucking on a pacifier among full-term infants as early signs of exposure-related changes in neurological function (67). One study reported adverse effects of DINP on the psychomotor skills of children exposed *in utero* (68).

Early-life exposure to DEHP, MEP, and MCPP has been reported to affect cognition in 3-year-old children (69), Exposure to MnBP has, in turn been associated with attention-deficit hyperactivity disorder (ADHD) (70). Similarly, a study in US children has associated phthalate exposure with ADHD-like behaviour and autism spectrum disorder, including emotional hyperreactivity, aggression, and impaired working memory, which was more prevalent in girls (71, 72). Speaking of infant girls, their exposure to HMW phthalates has also been associated with impaired orientation and quality of alertness, whereas LMW phthalate exposure in boys has been associated with impaired motor performance (73).

Immunotoxicity

As xenobiotics, phthalates can highly affect the immune system. They can induce pro-inflammatory cytokine release and therefore promote inflammation-related diseases (74) and increase the risk of developing allergies and asthma (75), which has been reported to be structure-related (76).

DMP can impair the function of erythrocyte and its antioxidant defence system (77). Another way for it to interfere with the immune system is by triggering mitochondrial dysfunction, which can lead to immunosuppression (78). The first controlled human exposure study (79) reported that inhalation of DBP exacerbated allergen-induced lung dysfunction and had immunomodulatory effect in the airways of allergic individuals.

Phthalates and cancer

Many studies showed that phthalates have tumorigenic activity affecting different signalling pathways (80, 81). Phthalate exposure has been associated with skin, liver, prostate, thyroid, and breast cancer (80, 82, 83), increased vascular endothelium growth factor (VEGF), angiogenesis, and tumour progression (84). Luo et al. (85) have provided evidence that DEHP affects cancer-stem-cell signalling pathways in the colon and thus promotes the progression of colorectal cancer. These findings have been corroborated by another study (86) reporting that phthalates enhance colon cancer cell metastasis and even chemotherapeutic drug resistance by increasing cancer cell stemness.

Phthalates and gene expression

Ling et al. (87) reported different effects of phthalates on mRNA translation/protein synthesis. BBP seems to directly inhibit mRNA translation *in vitro*, whereas its impact *in vivo* reveals a more complex pattern depending on concentration and whether translation is cap-dependent or independent. MEHP, on the other hand, seems to inhibit mRNA translation regardless. Both BBP and MEHP, however, promote mRNA translation in cancer cells.

PHTHALATES IN MEDICAL DEVICES

Certain medical procedures such as blood transfusion, intravenous (IV) drug or total parenteral infusion, enteral nutrition, haemodialysis, or cardiopulmonary bypass involve exposure to phthalates contained in medical devices made of polyvinyl chloride

(PVC) (10, 15, 88, 89), DEHP in particular. Its release from medical devices, most often into the bloodstream, may exceed tolerable intake and cause serious harmful effects (22, 23). Different plastic materials of medical devices release phthalates differently: indwelling tubing can leak 21 % of total DEHP content in 24 h of use, especially in lipophilic solutions such as parenteral solution or blood (14, 90, 91).

Of particular concern is exposure in preterm neonates in intensive care units, who are in constant contact with feeding tubes, endotracheal tubes, and umbilical catheters (12, 13, 15, 50) and whose urinary phthalates concentrations are significantly higher than in full-term infants (92–94). Higher phthalate levels have also been reported in infants undergoing surgical repair of congenital heart defects. Gaynor et al. (94) reported higher preoperative levels than those maternal and even higher after surgery and expressed concern about the risk for exposed infants of developing neurobehavioral disorders later in life. The expert panel of the US National Toxicology Program's Center for the Evaluation of the Risks to Human Reproduction assessed that, back in 2005, intensive care infant exposure to DEHP was two to three orders of magnitude higher than that of the general adult population and approached the lowest observed adverse effect levels (LOAEL) reported by animal studies (14–23 mg/kg a day) (43). In adults and children on indwelling medical devices receiving intensive care urine and blood DEHP metabolite levels were reported to reach 10 μmol/L (95).

Several studies suggest that phthalate exposure is associated with the intensity and duration of invasive medical procedures (15, 88). In adults, the highest short-term phthalate exposure is associated with blood transfusion and extracorporeal membrane oxygenation (ECMO), whereas the highest chronic treatment exposure is associated with haemodialysis (96).

Besides medical devices, Messerlian et al. (92) have pointed to aqueous gel for obstetrical ultrasound in pregnancy as an unrecognised source of maternal and foetal exposure to phthalates. *In utero* exposure is likely, as phthalates cross the placental barrier and have been detected in the cord blood and amniotic fluid, but consequences of exposure in this critical period of development do not manifest themselves until later in life (12). Prenatal and early infancy exposure to HMW phthalates (most prevalent in neonatal intensive care units, DEHP in particular) can affect multiple domains of neurodevelopment, functional performance, attention, and motor reflexes and increase the risk of shortened anogenital distance and cardiac malformation. Exposure to DEHP during the third trimester has been associated with preterm birth, cognitive, motor, and executive function disorders and behavioural changes such as hyperactivity and autism spectrum disorders during middle childhood (12, 13, 94, 97). Iatrogenic exposure to DEHP in 4-year children after intensive care was specifically associated with impaired attention and, to a lesser extent, with impaired motor coordination (98). One study in a neonatal intensive care unit also showed improvement in hepatobiliary function following a switch to DEHP-free infusion systems (99).

While the European Commission has set specific migration limits for plastic materials and articles in contact with food (100), no such limits have been set for medical devices. One study (101) of plasticiser migration from infusion bags, however, showed higher DEHP levels than those set in the Regulation No. 10/2011//EC (100), even though the inner solution was a purely aqueous medium. Moreover, their levels in outdated bags kept for three years in conditions set by the International Conference of Harmonization (ICH) were even 10 times higher than usual (101).

ECMO is another medical intervention with a high risk of exposure to plasticisers. Blood is in contact with PVC lines with high flow rate (5 to 6 L/min) and mechanical strain at 37 °C for longer periods of time, which all are conditions favouring plasticiser migration (102). One study (103) showed considerable amounts of DEHP and its metabolite MEHP in a patient on ECMO. Their levels seem to correlate with runtime and amount of cannulas and membranes used during treatment. Another study (104) also suggests that high DEHP exposure is associated with high blood bilirubin, which points to liver dysfunction. Starting the ECMO treatment often triggers a complex and immediate inflammatory reaction, further aggravated by DEHP and phthalates in general, as they have pro-inflammatory properties and promote inflammation-related diseases such as asthma, obesity, type II diabetes, and coronary artery disease (90, 102). Fortunately, Bouattour et al. (88) report that air humidification may decrease volatile DEHP levels in ventilation air, probably due to DEHP low polarity, and that exposure to phthalates from respiratory medical devices may not be as high as from other devices.

Previous reports suggest that acute or chronic exposure to phthalates may affect wound healing, as phthalates interfere with key immune cells and induce pro-inflammatory response. A study in mice exposed to phthalates at levels observed in humans (90) showed greater inflammation reaction, cardiac dilation, and reduced cardiac function, suggesting that phthalates released from medical devices may impair post-surgery healing and that the post-surgical patients may be particularly sensitive to phthalate exposure.

Plasticisers, DEPH in particular, are used in the production of blood bags and tubings for blood collection, labile blood product (LBP) processing, and transfusion. DEPH is good for storing red blood cells, as it keeps their membranes intact but it migrates into LBP and eventually comes into contact with patients. Replacing it with alternative plasticisers for LBP storage is not a simple solution, as their metabolites can be cytotoxic and affect the quality of the red blood cells and platelets (105–107) (see the section Alternative plasticisers for more detail). Another, more common solution is mechanical rinsing of stored blood prior to transfusion, whose primary purpose is to clean the bags from electrolytes. The second positive effect of rinsing is that it reduces both DEHP and MEHP concentrations (108).

Another source of exposure are face masks, particularly prominent during the COVID-19 pandemic, as recent studies reported several phthalates in them and raised the issue of exposure,

especially in vulnerable populations such as the elderly, children, and pregnant women (109, 110).

REGULATION OF PHTHALATES

Several European documents regulate the use of certain phthalates as plasticisers in consumer goods and health products. Phthalates have been recognised and categorised as carcinogenic, mutagenic, or toxic to reproduction ever since the Council Directive 67/548/EEC of 27 June 1967 (111) dealing with the classification, packaging, and labelling of dangerous substances.

Phthalates in medical devices have first been addressed in Annex I of the Council Directive 93/42/EEC of 14 June 1993 (112), requiring that medical devices containing phthalates be labelled as such. Also, if such devices are intended to be used in children or pregnant or nursing women, the manufacturer must provide a specific justification for their use.

In 2005, the EU banned DEHP, DBP, BBP from toys and childcare items (113), and in 2009, these bans entered the REACH Annex XVII (as entries 51 and 52). As time went by, more and more phthalates were recognised as unsafe. Currently 14 phthalates are on the REACH Authorisation List, which means that their use will be banned unless the European Commission allows a specific company to continue their use (114).

The most common plasticiser in flexible PVC medical devices, DEHP, has been classified as carcinogenic, mutagenic, or toxic for reproduction (CMR 1b) by the EU Regulation 1272/2008 since 2008 (115). In 2015, the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) expanded the 2008 classification with an updated opinion that replacement of DEHP with alternative materials should be considered, taking into account their efficiency in the treatment and their toxicological profile and leaching properties (116). The new EU Regulations 2017/745 (6) on medical devices, in effect since 26 May 2021, and 2017/746 (7) on *in vitro o* diagnostic medical devices, in effect since 26 May 2022 specify that CMR and endocrine disrupting (ED) substances are allowed in concentrations above 0.1 % weight by weight (w/w) only when justified pursuant to Section 10.4.2 of Annex I Chapter II. The justification is to be based on the latest relevant Scientific Committee guidelines as well as on estimation of patient/user exposure and possible alternative substances, materials, or designs claiming that such substitutes are inappropriate.

ALTERNATIVE PLASTICISERS

The most common safer plasticiser alternatives to phthalates are tri-octyl trimellitate (TOTM), di-isononyl cyclohexane-1,2-dicarboxylate (DINCH), di-isononyl phthalate (DINP), di-(2-ethylhexyl) terephthalate (DEHT), di-(2-ethylhexy) adipate (DEHA) and acetyl tri-*n*-butyl citrate (ATBC) (89, 102, 117). A recent study by Malarvannan et al. (99), however, still reports the dominance of DEHP, followed by DEHA, DEHT, TOTM, and ATBC, sometimes within the same device. Other alternative plasticisers, such as DINCH, DINP, DPHP, and DiDP were detected in no more than 5 % of the investigated samples. Another study (117) showed predominance of TOTM in hospital devices, with DEHP present at trace levels.

TOTM seems to be poorly absorbed following oral exposure, but data on intravenous exposure are still scarce (118). According to Eckert et al. (10), its mean migration is about 350 times lower than that of DEHP and it has low absolute mass loss. One study of TOTM release during ECMO therapy (102) showed a weak leak at non-cytotoxic doses, lower than the derived no-effect level (DNEL). Another *in vitro* study on L929 cells (119) found no cytotoxic effects of TOTM and its corresponding metabolite MOTM.

Moreover, the toxicological profile of TOTM seems to be significantly more favourable than that of DEHP (10). Another interesting observation made by Eckert et al. (10) is that DEHP and TOTM migration was lower with devices kept in storage for several weeks before use. The authors wonder whether it would be better to use PVC medical devices stored for longer than the fresh ones in high-risk patients, especially for critical interventions such as cardiopulmonary bypass.

Acetyl triethyl citrate (ATEC) and ATBC were also investigated as alternatives for DEHP. One study (120) found the former a better alternative, as it is less likely to induce anti-androgenic effects.

Urine samples stored at the German Environmental Specimen Bank (ESB) from 1999 to 2017 showed increasing presence of di(2-ethylhexyl) terephthalate (DEHTP) (121), but DEHTP exposure gives no reason for immediate concern, yet it warrants close monitoring in the future.

An *ex vivo* study (122) showed high DEHA migration rates from haemofiltration systems and concluded that DEHA might not be the best alternative plasticiser for CVVH tubings, considering that its primary metabolite monoethylhexyladipate (MEHA) can reach cytotoxic levels in patients undergoing the procedure. This cytotoxic effect of MEHA was also reported by Eljezi et al. (119) at the concentration of 0.05 mg/mL. Another study reported 106 times higher DEHA migration than that of TOTM (117).

Another alternative plasticiser with a distinctly lower toxicological potential than DEHP, tri-2-ethylhexyl trimellitate (TEHTM), was found to have a comparatively low resorption rate and a rather slow metabolism (to DEHTM and MEHTM) and excretion rate (123). Eckert et al. (113), in turn, evidenced low TEHTM levels in the blood of children after cardiac surgery, whereas DEHP from blood bags was significantly higher.

Another interesting alternative to DEHP is DEHT because of its low migration from medical devices and lower toxicity. However, its metabolite 5-OH-MEHT has a potential endocrine-disrupting effect (124).

One study of DINCH and DINP primary unconjugated metabolites on a L929 cell line (125) has shown that at concentrations

of 0.01–0.1 mg/mL they are more cytotoxic than their parent compounds, save for DINP's MMeOP. Among the secondary DINCH and DINP metabolites, however, only 7-oxo-MMeOCH showed cytotoxicity at 0.1 mg/mL after seven days of exposure. Another study (126) showed DINCH-induced cytotoxicity in human kidney cell lines after 24 h of exposure and transient oxidative DNA damage in liver cells exposed for 3 h. However, a German study (127) based on data from urine analysis in samples collected from young adults concluded that the median daily DINCH intake calculated for 2017 was 4,310 times below the tolerable daily intake (TDI). Even though this finding seems reassuring, the constant increase in DINCH exposure between 1999 and 2017, calls for its close monitoring, according to the study authors.

There are several other studies that call for collecting larger datasets regarding phthalate leachability and safety (89, 117, 128, 129). These data, including migration, leaching, and route-specific toxicity of alternative plasticisers will help to better weigh the risks and benefits of their use in medical devices (118).

As alternatives go, one is the use of plasticiser-free silicone tubing. However, Eckert et al. (10) showed a considerable loss of silicone mass from tubing over time, probably owed to the migration of siloxanes.

CONCLUSION

It is clear that all medical devices included in this review are of vital importance for patients and that the benefits still outweigh the risks. However, we cannot ignore additional risks for vulnerable groups of patients, neonates, infants, and pregnant women. Here we would also like to acknowledge potential risks for healthcare professionals, which we did not include in this review, but which deserve more attention in the future.

Future research, we hope, shall also shed more light on the risks and benefits of phthalate replacement with safer alternatives in medical devices, but until that time, phthalates will remain in use.

Conflicts of interest

None to declare.

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Medicinski proizvodi kao izvor izloženosti ftalatima

Ftalati su esteri ftalne kiseline, koji se koriste kao plastifikatori u velikom broju proizvoda kako bi poboljšali njihovu fleksibilnost, mekoću i rastezljivost. Uvelike se primjenjuju u proizvodnji medicinskih proizvoda, što stvara zabrinutost zbog migracije ftalata s proizvoda i njihova utjecaja na ljudsko zdravlje. Pregled objavljenih znanstvenih radova upućuje na povezanost ftalata s poremećajem reproduktivnog i endokrinog sustava, astmom, pretilošću, poremećajima u neurološkom razvoju, negativnim učincima na dišni sustav i toksičnim učincima na nekoliko organa, uključujući jetru, štitnjaču, bubrege i pluća. Cilj je ovoga preglednog rada sažeti dostupne zaključke članaka o migraciji ftalata s medicinskih proizvoda tijekom različitih medicinskih postupaka te o mogućem utjecaju na ljudsko zdravlje. U istraživanje su uključeni i članci o alternativnim plastifikatorima s nižom stopom migracije i sigurnijim profilom kako bi se utvrdio mogući sigurniji pristup medicinskim postupcima. Zaključci upućuju na otpuštanje ftalata u velikom broju različitih kritičnih, čak i kroničnih medicinskih postupaka, što može ozbiljno utjecati na zdravlje pacijenata. Za sada nema dovoljno podataka o udjelu pojedinih ftalata u proizvodnji medicinskih proizvoda ni o migracijskoj stopi i utjecaju na zdravlje alternativnih plastifikatora.

KLJUČNE RIJEČI: ljudska izloženost; plastifikatori; poremećaj reproduktivnog sustava; toksikologija; zakonska regulativa