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A review of alternatives to di (2-ethylhexyl) phthalate-containing medical devices in the neonatal intensive care unit

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Abstract

Objective—To conduct an extensive literature and toxicological database review on substitute compounds and available alternative medical products to replace polyvinyl chloride (PVC) and/or di(2-ethylhexyl) phthalate (DEHP), and conduct a DEHP-medical inventory analysis at a large metropolitan neonatal intensive care unit (NICU).

Study Design—A systematic search for DEHP-free alternative products was performed using online databases. An informal audit of a large metropolitan NICU was undertaken in 2005 and 2006; 21 products were identified that could potentially contain DEHP. Availability of DEHP-free alternatives was determined through company websites and phone interviews.

Result—Two alternative approaches are available for replacing DEHP in NICU medical products: (1) replacement by DEHP-free plasticizers; and (2) replacement of PVC entirely through the use of other polymers. Both approaches seem to provide less harmful substitutes to DEHP, 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 DEHP-free; six consisted of alternative polymers and four of alternative plasticizers. Of the remaining 11 products, only three were available without DEHP at the time of the audit.

Conclusion—Because of significant data gaps, systematic toxicological testing of DEHP-free alternatives is imperative. Continued development of alternative products is also needed.

Keywords

di (2-Ethylhexyl) Phthalate; alternative plasticizers; polyurethane; polyethylene; silicone; neonatal intensive care unit

Introduction

Di(2-ethylhexyl) phthalate (DEHP) is the predominant plasticizer added to rigid polyvinyl chloride (PVC) to impart flexibility,[1] temperature tolerance, optical clarity, strength and resistance to kinking.[2] It is found in numerous medical devices and can comprise between 20 and 40% of the final polymer weight.[2] As DEHP does not covalently bind to the PVC matrix, it can leach into solution with a rate dependent upon temperature, storage time, solution flow rate, the amount of DEHP in the PVC product and the lipophilicity of the solute.[3–16] Several studies have found that infants in the neonatal intensive care unit (NICU)

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Conflict of interest
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who undergo multiple medical procedures may be exposed to levels two to three orders of magnitude higher than the average daily adult, particularly when undergoing high-DEHP exposure procedures that require hours or days, such as continuous indwelling umbilical vessel catheter (UVC) and gavage tubing, endotracheal intubation and intravenous hyperalimentation by central venous route.[17–20] This is of concern as DEHP, and its more active monoester mono-(2-ethylhexyl) phthalate (mEHP), exert an effect as anti-androgens, which have demonstrated adverse reproductive and developmental effects in experimental and preliminary epidemiological studies.[2,21–36] In addition, a recent study found that use of infusion systems containing DEHP for total parenteral nutrition (TPN) was associated with a 5.6-fold increase in risk of cholestasis among NICU infants and that the incidence of this hepatobiliary dysfunction declined from 50 to 13% after switching to DEHP-free infusion systems.[37]

DEHP exposure in the NICU can be reduced either by substituting another plasticizer for DEHP in the PVC or by substituting the PVC entirely with another 'PVC-free' polymer.[14,15] Decreased DEHP migration can also be achieved by coating the inner liner of PVC tubing with a leach-resistant substance, such as heparin.[38] Moreover, a decrease of up to 40% in patient exposure to DEHP can be obtained by diminishing the surface area of certain medical devices, such as an extra-corporeal membrane oxygenation circuit.[38] Furthermore, substitute polymers could avoid the known lifecycle hazards of PVC linked to a carcinogen-laden manufacturing process (ethylene dichloride and vinyl chloride monomer) and downstream toxicants emitted from incineration, including hydrochloric acid, dioxins and furans.[14,15,39] Although potential occupational risks from DEHP-alternatives or their monomer/intermediate materials are not reviewed in this study, the health effects from the production and incineration processes of these alternatives should be considered. Although lifecycle hazards of DEHP-alternative materials need to be assessed and considered, they are outside the scope of this review.

The increasing availability of alternative medical products is due in part to a growing awareness of DEHP health effects raised by academic and advocacy groups such as Health Care Without Harm (HCWH) and the Sustainable Hospitals Project, as well as the issuance of international health and policy notifications by the European Union (EU), Health Canada and the United States Food and Drug Administration (FDA).[40–44] However, available toxicological data on these substitutes are limited or otherwise difficult to compare because of inconsistent research methods. It should be noted that data are limited on some chemical substances, especially those used in proprietary materials, as companies do not have to reveal or test these substances under the Toxic Substances Control Act of 1976 (TSCA), rendering a comprehensive toxicity assessment difficult.[45] To our knowledge, other publications evaluating alternatives to DEHP in the medical setting have been limited in scope with regard to toxicity data, substitutes covered (that is, DEHP-free plasticizers only), or focused on non-medical DEHP-free alternatives.[14,15,46,47] We have therefore conducted an extensive review of the literature and toxicological databases on substitute compounds and available alternative medical products both in United States and Europe to replace PVC and/or DEHP in NICUs. In addition, a small-scale analysis of the neonatal medical supply inventory at a large metropolitan NICU and a survey of medical suppliers on available DEHP substitutes were carried out to assess the potential for implementation of alternative practices.

Methods

A systematic database search and review of the literature for DEHP-free alternative products and substitute compounds both for PVC uses generally, and medical products specifically, was performed using online databases (Medline, PubMed, Google Scholar, National

Toxicology Program, National Library Medicine's Hazardous Substances Database and Integrated Risk Information System). The search strategy included the use of the following keywords: adipate, alternative, citrate, clinical, di(ethylhexyl) adipate (DEHA), di(2-ethylhexyl) phthalate (DEHP), di(isononyl) cyclohexane 1,2-dicarboxylate (DINCH), ethylene-vinyl acetate copolymer, medical, neonatal, neonatal intensive care unit (NICU), *O*-acetyl tributyl citrate (ATBC), polyurethane (PUR), silicone, tri-2-ethylhexyl trimellitate (TETM).

Subsequent to contacting a neonatologist in the NICU, we toured a large metropolitan NICU to learn about product use and obtain an inventory of currently used medical products for the purpose of assessing DEHP prevalence in these products. We assessed 21 medical products in the following six categories based on their potential for DEHP exposure during neonatal procedures as defined by the FDA: (1) enteral feeding sets; (2) feeding tubes/accessories; (3) intravenous (IV) products (including TPN); (4) respiratory therapy; (5) catheters; and (6) dialysis equipment.[48,49] We conducted research on medical supply manufacturing companies through the use of company websites, as well as phone interviews to assess availability of DEHP alternatives. Subsequently, research was conducted to identify DEHP-free alternatives offered by the supplier providing the specific DEHP product.

Results

Two alternative methods can replace DEHP in medical products. One method is to replace only the DEHP in PVC with a DEHP-free plasticizer to confer flexibility to a rigid polymer. Although DEHP leaching can be decreased or prevented using DEHP-free plasticizers, the lifecycle hazards associated with PVC are not addressed in this method.[13] A second alternative is to replace the PVC entirely through the use of another naturally flexible polymer. As these PVC-free substitutes may require additives to impart desired qualities on the polymer, the leaching of these additives must be considered and a safety assessment of each alternative is imperative before finalizing the choice of material.[15,48] Further, although existing literature provides at least some indication for weighing potential hazards through comparisons of no observed adverse effect levels (NOAEL) or lowest observed adverse effect levels (LOAEL), sufficient exposure assessment under conditions of use is often missing. Therefore, it is not currently possible to conduct an adequate risk assessment of some alternative products. In this section, specific alternative DEHP-free plasticizers and PVC-free polymers will be discussed and relevant toxicological data is reviewed. These data are summarized and shown in Table 1.

DEHP-free plasticizers

Existing literature identifies carboxylates, adipates, citrates and trimellitates, specifically DINCH, DEHA, ATBC, TETM and polyester (polyadipate) as the primary alternative plasticizers to DEHP in medical products.[7,13] The most comprehensive data are available for DEHA.[14,56] Although some literature on potential DEHP-free plasticizers for medical uses also includes phosphates, benzoates and aliphatic dibasic esters, these plasticizers were not considered in this review because of lack of toxicological data compared with DEHP.[13,14] Substitute phthalate plasticizers, such as di-isononyl phthalates (DINPs) are also available. However, given the recent European Parliament decision to prohibit the use of phthalates in cosmetics, children's products and toys, coupled with the fact that DEHP is the only phthalate approved by the European Pharmacopoeia for medical use in PVC, the substitution of DEHP with another phthalate was not considered.[13,57,58]

Di(isonyl)cyclohexane-1,2-dicarboxylate

DINCH is the most recently developed alternative plasticizer for sensitive applications and is trademarked as Hexamoll DINCH by BASF, Ltd (Cheshire, UK).[41] DINCH is obtained by the hydrogenation of the benzene ring in *o*-phthalates (as is DEHP).[48] Although the molecular weights of DINCH and DEHP are comparable, structural differences between the two leads to a lower PVC interaction with DINCH.[48] BASF uses DINCH in the manufacturing of enteral and hemodialysis tubing, bags, respiratory tubes, catheters, gloves and breathing masks.[49] In 2007, BASF expanded DINCH production to 100 000 tons up from 25 000 tons in 2002.[41]

Research shows DINCH migration into enteral feeding solutions is eightfold lower than DEHP migration.[59] Because of similar viscosities and mechanical properties, DINCH substitution for DEHP does not require costly changes in the plasticizer content or in the use of viscosity modifiers.[48] Brought to market as a 'sensitive alternative' to DEHP, this new plasticizer has undergone extensive toxicological testing.[46] BASF states that DINCH has an 'excellent toxicological profile' with no reproductive hazards, such as testicular toxicity, fertility impairment, teratogenicity, endocrine disruption, and no evidence for perixosome proliferation, carcinogenicity or environmental hazards.[49] Although testing showed no maternal or developmental toxicity, repeated dose and multi-generational studies in rats found increased liver, kidney, thyroid and testicular weights in all groups in the repeated dose study.[46] However, it should be noted that although these studies are summarized in the SCENIHR report (2007), the experimental design does not conform to the guidelines of the Organisation of Economic Co-operation and Development (OECD).[60] In the multi-generational study, although there was a significant decrease in male anogenital index and anogenital distance in the high-dose group, these were not considered biologically significant by study authors as other parameters like descending testes, testes weight and sperm were not affected.[46] On the basis of these studies, a NOAEL of 1000 mg kg^{-1} per day was established for fertility, developmental and reproductive toxicity, at 100 mg kg^{-1} per day for thyroid hyperplasia, and at 107 mg kg^{-1} per day and 389 mg kg^{-1} per day for kidney effects in males and females, respectively.[46]

Di(ethylhexyl) adipate

Adipates are produced with various alcohol groups and are diesters of aliphatic dicarboxylic acids.[14] Their classification as low temperature plasticizers make adipates a preferred plasticizer for cold solutions storage (for example, blood).[14,47] DEHA is similar in structure and metabolism to DEHP, is extensively used in household plastic food contact materials, and is expected to become widely used in medical products and packaging.[14,27] The available data on DEHA indicate that the compound is more lipophilic than DEHP, has a threefold greater potential to leach relative to DEHP, and has the highest migration potential of all DEHP-free PVC plasticizers described in this section.[14,46]

DEHA does not seem to cause genotoxicity, and although a slight irritant to rabbit skin, DEHA does not have sensitization effects and has a very mild acute toxicity.[14,53] Because of limited evidence of carcinogenicity in animals, DEHA is classified as a Category 3 carcinogen by the International Agency of Research on Cancer (IARC).[50] In repeated dose toxicity studies, DEHA produced dose-dependent changes in body and liver weights of males, females and offspring, as well as significantly increased incidence of liver tumors in female mice.[61–64] However, liver tumors were not anticipated to be correlated with human exposures as they are induced by peroxisome proliferation, a mechanism involving hormone receptors expressed at much lower levels in human livers than in mice.[53]

In terms of reproductive toxicity, unlike DEHP, DEHA has not shown adverse testicular or anti-androgenic effects (at doses of up to 1200 mg kg^{-1} bw per day).[22,27,33,65–67] Studies have shown that DEHA induces mild to moderate developmental toxicity at 400 and 800 mg kg^{-1} bw per day, respectively, resulting in a prolonged gestation period, smaller pup size and an increased incidence of postnatal death.[66] Although the molecular structures of DEHP and DEHA are analogous, studies have confirmed that DEHA does not have endocrine effects similar to DEHP.[22] In other animal studies, a maternal NOAEL was set at 170 mg kg^{-1} per day and the NOAEL for the critical endpoint of fetotoxicity was set at 28 mg kg^{-1} per day. At this dose no ossification and kinked or dilated ureters in the fetuses resulted.[14,50–52] Despite these findings, the 2007 EU-SCENIHR opinion suggests the establishment of a NOAEL of 200 mg kg^{-1} per day for developmental and fetotoxicity.[46] However, the rationale for this assessment was not available and in our opinion, further research addressing the reproductive toxicity of DEHA is warranted given the lower NOEALs in other studies.

O-acetyl tributyl citrate

Citrates are citric acid esters and represent another group of plasticizers. ATBC is a non-volatile compound that has higher water solubility and is less lipophilic compared with other plasticizers, including phthalates.[14,46,68] However, ATBC was found to migrate into enteral feeding solutions in significant quantities.[46,59] Although ATBC is currently used in many products including cosmetics, flavoring agent in foods, toys, packaging, printing inks and adhesives, because of its anti-coagulant properties ATBC is medically used mainly in the production of blood bags and medical tubing.[14,15,46] Exposures to NICU infants seem to be primarily from pacifiers containing ATBC.[15]

Current data indicate that ATBC has no or low genotoxicity and low acute oral toxicity.[53] Although moderate eye irritation has been observed in animals, ATBC was not found to cause skin irritation or sensitization.[14] Repeated dose toxicity experiments demonstrated hematological and biochemical changes that resulted in increased liver weight.[14,53,54] The critical effect in experimental rats seemed to be reproductive toxicity resulting in decreased body weight.[46,53] The lowest reported NOAEL was 100 mg kg^{-1} bw per day for repeated dose gavage toxicity and reproductive toxicity.[53] Effects from prolonged exposure are largely unknown and therefore further research is critical.[14]

Tri-2-ethylhexyl trimellitate

TETM is a group of esters of trimellitic acid (1,2,4-benzene tricarboxylic acid) generally known to have a higher molecular weight and lower migration potential in aqueous solutions when compared with other plasticizers.[14,46] TETM's additional ester group makes it more hydrophobic than DEHP.[55] Studies have systematically found significantly less or no leaching of TETM compared with DEHP from medical devices such as hemodialysis tubing and blood platelet bags into human and calf serum, respectively.[69–73] The most common applications of TETM are in medical products, specifically blood bags and infusion sets, packing, cables, floor and wall coverings.[14,47]

TETM has been found to have low acute oral and dermal toxicity in animal studies, but was more toxic via inhalation and should be classified as harmful by inhalation.[14] Available data indicate TETM is not mutagenic nor carcinogenic.[14,74] Although slight skin irritation in animals has been observed, there was no sensitization from TETM.[14] In a human dermal study on 203 volunteers, TETM produced slight erythema in four individuals and no evidence of sensitization.[75] Chronic toxicity studies in rodent bioassays showed slightly increased liver weights and liver enzymes, as well as slight induction of peroxisome proliferation.[14] Data show that the degree of liver toxicity was far less in animals treated

with TETM compared with DEHP.[46,55] The lowest observed adverse effect level for increased liver and spleen weight was 42 mg kg^{-1} bw per day following injections in dogs for 14 days, and 184 mg kg^{-1} bw per day following oral exposure in rats.[14]

Reproductive and developmental toxicity were studied by Japan's Ministry of Health in a gavage study in rats at three doses (100, 300 and 1000 mg kg^{-1} per day) of TETM.[46,55] Examination of testes found decreased spermatocytes and spermatids in males at the two highest dose levels. No effects of TETM were detected on body weight, ovaries, reproductive organ weights, reproductive ability of maternal dams and no changes in viability or body weight were detected in offspring. On the basis of this study, the NOAEL for males is 100 mg kg^{-1} per day and 1000 mg kg^{-1} per day for females and offspring.[46,55] Although data suggest TETM to be a promising plasticizer, and efforts are underway to switch to this seemingly safer and lower-migration DEHP-alternative, more consistent research on reproductive and development toxicity is needed before TETM can be routinely used as a PVC plasticizer.[14,72]

Polyester (Polymeric adipate/polyadipates)

Polyadipates are typically polymers based on divalent acids condensed with diols that have been used as 'polymeric (or polyester) plasticizers' in feeding tubes since the early 1980's and have been approved by regulatory authorities.[7,14,76] Although a broad range of molecular weights can be obtained based on use through polycondensation, the highest molecular weight polyesters have the lowest potential for migration into a lipophilic substance of all the plasticizers discussed.[14] Polyadipates are promoted by chemical companies in Europe as a low-cost alternative to DEHP for short-term use of gastric tubes, whereas polyurethane or silicone devices are suggested for long-term tube feeding because of their durability.[76]

A recent study that measured extraction of DEHP and polyadipate from PVC nasogastric tubes through juice and feeding solution, found that polyadipate leaching was 10 times lower than that of DEHP in the feeding solution group and 100 times lower in the gastric juice group.[76] This study suggested that polyadipate nasogastric tubing should be used as an alternative product in order to reduce DEHP exposure in NICU. However, critical data on developmental and reproductive toxicity for polyadipates are unavailable and potential side effects have not been assessed.

PVC-free alternatives in medical products

Alternative polymers to PVC that do not require a phthalate plasticizer for flexibility are therefore inherently DEHP-free while avoiding the hazards of dioxin formation and other hazardous organochlorine by-products associated with PVC production and disposal by incineration.[13,56,77] In addition, polymers treated with additives such as antioxidants, avoid the introduction of reactive groups in the polymer skeleton that would lead to a less stable material.[14] Polymers deemed as viable alternatives to replace PVC in the medical bag market (for example, IV solution, blood and specimen bags) include polyolefins, either polyethylene (PE) or propylene, and ethyl vinyl acetate (EVA). The most suitable polymers for the replacement of PVC in medical tubing seem to be polyolefins, PUR, EVA and silicone.[13–15] A short summary of the available toxicological and environmental data on each of these four polymers is provided in this section.

Polyolefins

Polyolefins are a class of polymers that include PE and polypropylene, and seem a viable polymer substitute to PVC for many applications in the long-term.[15] Because of processing ease, relatively low cost and durability, polyolefins are currently the most widely used

plastics in the world.[78] Polyolefins may also offer new benefits such as an inherently improved water–vapor barrier useful in packaging aqueous solutions.[77] Metallocene polyolefins have a narrow molecular weight distribution resulting in reduced need for additives, low leaching and migration potential, as well as superior physical qualities (that is, flexibility, clarity and tensile strength).[15] Polyolefin bags are used for the storage of blood platelets as an alternative to PVC.[79]

a. Polyethylene—PE is a thermoplastic polymer produced through a reversible process that allows the reshaping and reuse of materials. It is one of the most ubiquitously used polymers constituting plastic bags and plastic food film.[14] Because of insufficient epidemiological data, PE is not classifiable in its carcinogenicity to humans (IARC Group 3).[14] As a result of the low toxicity of PE and its monomer ethylene, medical use of PE has been extensive.[14]

A study examined systematic leaching of DEHP from several PVC co-extruded lines laminated with PUR or PE to prevent DEHP leaching, plus non-PVC perfusion lines, and found that co-extruded PVC/PU and PVC/PE lines leached comparable levels of DEHP to pure PVC lines (74 to 107 $\mu g\ m^3$) when used with a lipid emulsion. Pure PE perfusion lines, however, leached only a negligible fraction of DEHP (0.23 $\mu g\ m^3$) (see ref. 9). This study shows that co-extruded perfusion lines do not prevent DEHP extraction and suggest that hospitals, especially in the case of newborns, replace PVC and PVC co-extruded lines with available pure PU or PE alternative lines.[9]

In another recent study, lipid emulsions were administered intravenously via either PVC or PE infusion systems over 3 weeks to prepubertal rabbits at doses similar to those administered to human newborns.[80] The PVC-administered group showed liver toxicity and increased oxidative stress compared with the PE group. Symptoms such as hydropic degeneration, cell necrosis, fibrosis, multiple nuclear changes, and clustered and atypical forms of peroxisomes were found to be enhanced in the PVC group but were present to a minor degree in the PE group.[80] The authors concluded that DEHP from PVC could produce hepatobiliary dysfunction in newborns undergoing TPN, and suggested PE lines be used for newborns.[80]

b. Polypropylene—Polypropylene is a plastic made from propylene, a substance which has not shown evidence of carcinogenicity *in vitro.*[81] Propylene is soluble in water and exhibits low lipophilicity. Data are currently unavailable on the absorption, distribution or excretion of propylene in humans. Propylene is a respiratory toxicant through inhalation at high exposure levels in animal studies.[82] However, research is sparse on lifetime rodent toxicity studies and no data exist on long-term human toxicity or epidemiology studies.[81]

Polyurethane

PUR is a thermoset polymer, which unlike a thermoplastic polymer, undergoes an irreversible production process rendering its materials final.[14] To our knowledge, data on potential health effects of PUR have not been published.

Some durability data are available, however. Enteral feeding tubes are typically made from PVC, PUR or silicone, depending on its application.[15] Since percutaneous endoscopic gastrostomy (PEG) tubes are often used for many months or years, the durability of these tubes has an important role.[83] Research shows that PEG tubing and catheters made from PUR are more resistant to tube deterioration than silicone PEG catheters, suggesting that PUR should be the preferred long-term material for enteral feeding tubes used in the production of PEG catheters.[83,84] However, it should be noted that another recent and similarly small study showed that silicone tracheotomy tubes are superior to PUR.[85]

Regardless of this contradiction, both PUR and silicone are more durable than PVC endotracheal tubes and proposed as alternatives to PVC, especially in the NICU.[86]

Ethylene vinyl acetate

Ethylene vinyl acetate (EVA) is made from the co-polymerization of ethylene and vinyl acetate.[15] EVA has the ability to retain its properties of tensile strength, durability, clarity and flexibility over time. Through the modification of the vinyl acetate monomer, EVA can range from conventional thermoplastic to elastomeric (rubbery) state while increasing its overall polymer strength.[15,78] EVA is highly water soluble and is the least lipophilic among alternative compounds.[87] Because of its polarity, sheets of EVA can be welded with ease and its low sealing temperature results in lower processing costs.[15] EVA is widely used as a laminate in higher-end markets, as well as a drug-delivery device (for example, contraceptive device NuvaRing).[88] In the medical setting, EVA has been found to be more suitable for use in parenteral and enteral administration devices rather than in blood storage.[47]

Although there are toxicity data on the raw materials used in the production of EVA, our research did not find carcinogenicity or other relevant health data pertaining to EVA.

Silicone

Silicone is a polymeric compound containing polydimethylosiloxane monomers, in which silicone atoms are joined with oxygen to form chains. The remaining silicon valence electrons link mainly with methyl groups or with other organic groups.[89] Silicone has been widely used in medical devices including breast implants, tubing for drains, catheters, dialysis machines and blood oxygenators.[90] Much of the existing epidemiological data on silicone have come from the research associated with women's exposure to silicone through breast implants. However, a handful of recent studies focused on the health effects of silicone in medical devices such as catheters and enteral feeding tubes.[90] Data suggest that lipid uptake contributed significantly to the deterioration of the silicone tested, leading to device failure.[91] Baseline data aimed at characterizing the toxicological profile produced by treatment with silicone showed that there were no significant changes in the weight of the brain, liver, spleen, thymus, lungs or kidneys.[90] Data on developmental and reproductive toxicity are lacking but critical with the increased use of silicone in the medical device arena.

Case study results: DEHP-free medical devices in a metropolitan NICU

An initial audit in a large metropolitan NICU was conducted in November 2005 and a follow-up audit was conducted after 1 year in November 2006. Results of the case study are shown in Table 2. Within the 1-year timeframe between the first and second audit, a group of NICU nurses had led a campaign to switch away from one commonly used product, a DEHP-containing TPN solution set, to one made from PVC and trimellitate. The audit found that 10 of the 21 sampled NICU products (48%) were DEHP-free at the time of the second audit, whereas the remainder of the sampled products (52%) consisted of DEHP-containing PVC. Of the DEHP-free products, six were PVC-free and made from alternative polymers including PUR, polypropylene, silicone, polysulfone and Vialon (a Becton Dickinson, Franklin Lakes, NJ, USA) proprietary material), whereas the remaining four products are made from PVC with alternative plasticizers, namely trimellitate. Of the 11 products containing DEHP that were used in the NICU at the time of the second audit, we contacted the suppliers of that product and only three of the product types from that supplier were available without DEHP (for example, enteral and gastric tubing). Interestingly, since the time the audit was completed in 2006, two more DEHP-free products became available in 2008 from the relevant supplier.

Discussion

The existing yet incomplete toxicological and epidemiological data on DEHP-free alternative plasticizers and PVC-free polymers indicate they are potentially less harmful than neonatal exposure to DEHP, and can be considered suitable in medical bags and tubing, especially when used in high-exposure procedures. Although lifecycle analyses of DEHP alternatives are essential, because of the known environmental and health hazards related to the production and disposal of PVC, and the leaching potential from alternative DEHP-free plasticizers, a complete withdrawal of PVC in medical tubing and bags may be the most appropriate solution, especially when containing or transporting lipid solutions, and the use of PVC-free polymers may be the preferred alternative.[9,13,56,92,93] However, because of significant data gaps and the lack of consistent methods for comparing health and ecological impacts of compounds described above, a thorough analysis of these alternatives to PVC and DEHP is required.[13,15,77]

Hospitals are increasingly demanding PVC-free products thereby driving the research and development in the alternative polymer market.[13,77] European manufacturers and suppliers are heeding regulatory pressures and this demand is leading to increased development of PVC-free alternatives, although technically exacting products may not yet exist for every DEHP-containing product.[15,13] Another important consideration is that a comprehensive switch to DEHP-free products in a NICU may constitute a multi-year endeavor due to inherent contractual purchase agreements between supplying manufacturers/vendors, and hospitals. As new products with alternative plasticizers and polymers appear on the medical device market, it is important to weigh their potential health effects against those of DEHP, particularly in the NICU setting. Comprehensive sub-chronic and chronic toxicity studies on the alternative plasticizers and polymers are critical and overdue.[15] Given the increased susceptibility of neonates, as well as the known adverse health effects of DEHP, any DEHP-free alternative should be thoroughly evaluated based on comprehensive toxicological study, monitoring for long-term health effects and standards of safety, as well as its functional effectiveness, cost-efficiency and regulatory compliance.[79]

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Table 1

Migration potential and health effects of DEHP-free plasticizers and alternative polymers

Category	Compounds	Migration potential[a] (molecular weight)	NOAEL	Critical Effect
DEHP-free plasticizers	DINCH	Low (424.6) see ref. 48	Reproductive and developmental toxicity: 1000 mg kg^{-1} per day Thyroid hyperplasia: 100 mg kg^{-1} per day; see ref. 46	Nephrotoxicity/increased thyroid, kidney and liver weights.[46]
	DEHA	Highest (370.6) see ref. 14, 46	Reproductive toxicity: 170 mg kg^{-1} per day; Developmental: 28 mg kg^{-1} bw per day (200 mg kg^{-1} per day by EU)[14,50–52]	Developmental toxicity resulting in skeletal variations, kinked or dilated ureters.[14,50–52]
	ATBC	High (402.5) see ref. 14	Reproductive and repeated dose toxicity: 100 mg kg^{-1} bw per day; see ref. 53	1) Reproductive toxicity resulting in decreased body weights.[46,53] 2) Repeated dose toxicology: hemotological changes, biochemical changes and increased liver weights.[14,53,54]
	TETM	Lowest (but may contain DEHP) (546.8) see ref. 14, 46	Reproductive and developmental toxicity: 100 mg kg^{-1} per day for males, 1000 mg kg^{-1} per day for females and offspring[46,55]	Lung changes observed in rats from inhalation.[14]
	Polyadipate	Low[14]	No data	No data
PVC-free polymers	PE	No data	No data	No data
	PP	No data	No data	No data
	PUR	No data	No data	No data
	EVA	No data	No data	No data
	Silicone	No data	No data	No data

Abbreviations: ATBC, *O*-acetyl tributyl citrate; DEHA, di(ethylhexyl) adipate; DEHP, di(2-ethylhexyl) phthalate; DINCH, di(isononyl)cyclohexane-12-dicarboxylate; EVA, ethylene vinyl acetate; NOAEL, no adverse effect level; PE, polyethylene; PP, Polypropylene; PUR, polyurethane; PVC, polyvinyl chloride; TETM, tri-2-ethylhexyl trimellitate

[a] A key parameter in comparing plasticizers is potential for migrating out of the PVC polymer, however, only few data have been identified on migration potential for substitutes and testing was not standardized, therefore, we report only comparison levels, not values.

Table 2

Case Study of DEHP materials in Metropolitan NICU (2005–2006)

Product name-used in NICU	Manufacturer	Product no.	Type of product material[a]	Alternative product available[b]
1. Enteral feeding tubes (SETS)				
Enteral feeding tube for incubators	Vygon, Montgomeryville, PA, USA	Ref. 312.06	PVC (with DEHP) (durability: 3–5 days)[c]	PUR or Silicone (durability: 30 days)
36″ Enteral extension set	Philips Children Medical Venture, Monroeville, PA, USA	95017-E	DEHP-free PVC	Also available with PUR
2. Enteral feeding tubes/accessories				
Double lumen gastric tube (long-term tube)	Vygon	Ref. 340.10 (10fr-L.90 cm)	PVC (with DEHP) (durability: 3–5 days)[c]	Polyurethane or silicone (durability: 30 days)
ARGYLE Polyvinyl Chloride Feeding Tubes with SENTINEL LINE (16″)	Tyco-Kendall (Covidien), Mansfield, MA, USA	8888260604	ARGYLE PVC (with DEHP)[c]	No available alternative (20″ & 36″ PUR available, 2008)
8 Fr. Pediatric Feeding tube (42″)	CR Bard, Murray Hill. NJ, USA	0036420	PVC, latex-free[c]	No available alternative
3. IV Product				
BD Insyte-N Autoguard	Becton Dickinson, Franklin Lakes, NJ, USA	Ref. 381411/	Vialon DEHP-free	N/A
IV bag: 10% dextrose injection USP	Baxter, Deerfield, IL, USA	2B0163	VIAFLEX (PVC with DEHP)[c]	No available alternative (polyolefin blend available, 2008)
CONTINU-FLO Solution Set with 2 INTERLINK injection sites (for TPN use with lipids)	Baxter	new: 2H6519	DEHP-free PVC (TETM)	N/A
Microbore T-Connector Extension Set with 1 INTERLINK T-connector injection	Baxter	2N3326	DEHP-free PVC (TETM)	N/A
Tubing –Air eliminating (.2 micron) filter, 7″ minibore extension set	Churchill, Montgomeryville, PA, USA	AMS-427 or 952	DEHP-free, latex-free	N/A
3-Way Large Bore (lipid resistant) Stopcock	Baxter	2C6201	PVC-free (Polysulfone)	N/A
Standard Bore Extension Set (30″)	Baxter	2C5645	PVC (with DEHP)[c]	No available alternative (only microbore avail. DEHP-free; TETM)
Thoracic Catheter-Argyle/ARGYLE Trocar Catheter 10Fr × 9″ (23 cm)	Tyco–Kendall (Covidien)	8888561019	PVC (with DEHP)[c]	No available alternative
Syringe (common): MONOJECT PreFill I.V. Flush Syringes	Kendall REI (Covidien), Mansfield, MA, USA	8881570300	PVC-free (Polypropylene; saline filled; latex and preservative free)	N/A
4. Respiratory therapy				
Infant nasal CPAP Cannula	Hudson RCI, Research Triangle Park, NC, USA	1695	PVC (with DEHP)[c]	No available alternative
Portex extra length pediatric tracheostomy	Smiths Medical North America, Dublin, OH, USA	555035	PVC (with DEHP), Latex-free[c]	Available in silicone

Product name-used in NICU	Manufacturer	Product no.	Type of product material[a]	Alternative product available[b]
tubes (respiratory endotracheal tube)				
5. Catheters				
PICC Line (peripherally inserted central catheter) Epicutaneo E-Catheter (30 l cm, volume, ml (0, 12)	Vygon	24 g (2fr); 2184 (015345)	PVC-free (Silicone)	N/A
Umbilical catheter insertion tray (UVC)	Vygon	Order no. 1270.004	PVC-free (Polyurethane)	N/A
UVC-arterial tray	Kendall (Covidien), Mansfield, MA	160341	PVC-free (polyurethane)	N/A
Neonatal Kit w arterial line (common)	Hospira, Lake Forest, IL, USA	41-327-CA (similar item #425-86-05)	PVC (with DEHP), latex-free[c]	Polyethylene-lined IV bags/ tubing available
6. Dialysis, Peritoneal				
Peritoneal dialysis tubing-extended (rare) ‘MiniCap Extended Life PD Transfer Set (6′)	Baxter	5C4449	PVC (with DEHP)[c]	No available alternative

Abbreviations: DEHP, di(2-ethylhexyl) phthalate; PUR, polyurethane; PVC, polyvinyl chloride; TETM, tri-2-ethylhexyl trimellitate; TPN, total parenteral nutrition; UVC, umbilical vessel catheter.

[a] Information regarding medical product materials was obtained directly from the manufacturer’s website and/or via telephone communication with companies’ sales, medical, and/or regulatory affairs department.

[b] Alternative product availability is restricted to the medical company manufacturing the specific product sampled.

[c] Denotes DEHP products.

[3] In the duration of the case study, the NICU switched from Baxter Interlink system w duo-vent spoke (DEHP) to Non-DEHP CONTINU-FLO Solution Set with with 2 INTERLINK injection sites (for TPN use with lipids).