Polyvinylchloride, phthalates and packaging

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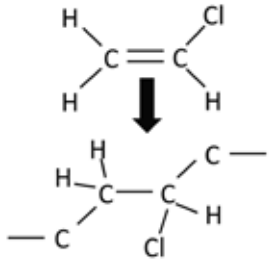
Plastics are synthetic resins, are either thermosetting or thermoplastic. Thermoplastic resins can be re-softened by heating, and include polyethylene (PE), polystyrene (PS), polypropylene (PP), and polyvinylchloride (PVC) which is very widely used in disposable medical devices.

Polyvinylchloride (PVC)

Vinyl chloride (CH_2=CHCl or chloroethylene) is polymerized by free-radical initiators to open the double bond and to link together vinyl chloride monomers, to form repeating units of polymers (Figure 1).

Figure 1
The chemical structure of vinyl chloride and PVC



PVC is a rigid structure at room temperature. Heating gives the molecules energy, widens the distance between between the molecules and softens the resin. To give PVC flexibility at room and body temperatures, plasticisers are added non-covalently to the PVC when molten and serve as molecular spacers so when cooled the polymer has a softness even at room temperatures. The most commonly used plasticisers are phthalates.

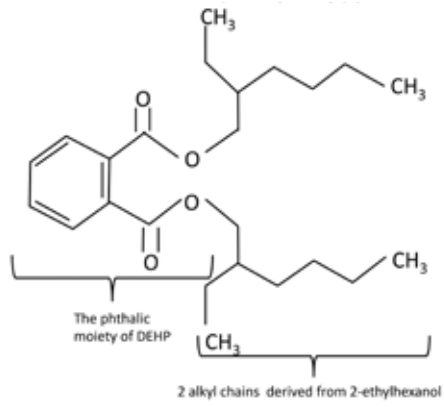
Phthalates

Phthalates are esters of phthalic acid, and are made by esterification of phthalic anhydride with variable chain length alcohols. Low molecular weight phthalates have three to six carbon atoms in their alcohol chain and high molecular weight phthalates have more than six carbon atoms. The longer the chain, the greater the permanency and durability of the plastic. The most commonly used phthalate in medical devices, such as intravenous cannulae, giving sets and blood product bags, have been Di(2-ethylhexyl) phthalate (DEHP), and less commonly, diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP).

Di(2-ethylhexyl) phthalate (DEHP)

DEHP (sometimes referred to as bis (2-ethylhexyl) phthalate) is the diester of phthalic acid and 2 ethylhexanol (Figure 2).

Figure 2
The structure of di(2-ethylhexyl) phthalate DEHP. The phthalic moiety is common to all phthalates; the pair of symmetrical aliphatic chains depends on the esterified alcohol



At room temperature it is a colourless, oil-soluble viscous liquid and is used to form up to 40% of the mass of the PVC product. The annual global production of DEHP is estimated to be 1–4 million tonnes.[1]

The absence of chemical bonding between the phthalate and the polymer allows leaching of the phthalate over time and typically makes the plastic more brittle.

DEHP and health

Environmental exposure to DEHP is inevitable in low levels, given the widespread use of PVC.[2] Animals exposed to DEHP develop renal papillary mineralisation, have an increased incidence and severity of chronic progressive nephropathy, hepatomegaly and hepatocellular tumours.[3,4] Long term exposure results in testicular atrophy and testicular tumours.[5]

'Within the EU, Directive 2005/84/EC effectively banned DHEP, benzyl butyl phthalate (BBT) and dibutyl phthalate (DBT) from children's toys and childcare articles.'[6]

Concern that it may be both a carcinogen, albeit in rodents, and impair spermatogenesis has encouraged toy manufacturers to use alternative plasticisers in plastics in the United States.[2] Within the EU, Directive 2005/84/EC effectively banned DHEP, benzyl butyl phthalate (BBT) and dibutyl phthalate (DBT) from children's toys and childcare articles.[6]

DEHP and plastic medical devices

Fluid filling and passing through medical devices has the potential to leach the phthalate into the patient, and this is dependent on the procedure and the lipophilicity of the fluid that comes into contact with the medical device, the PVC surface size, the temperature, flow rate and contact time.[7] DEHP is metabolised at multiple sites, including the intestine, to mono (2-ethylhexyl) phthalate (MEHP) and 2-ethylhexanol.[8] Human exposure is assessed by measuring the urinary excretion of MEHP.

The neonate and the developing foetus represent the most vulnerable phases of life with regard to developmental and reproductive toxicity. Neonates in the Neonatal Intensive Care Unit (NICU) are exposed to multiple medical-device-related DEHP exposure from feeding tubes, infusion tubing, umbilical catheters, PVC blood bags, transfusion tubing, and endotracheal tubes. In the Paediatric Intensive Care Unit (PICU) haemodialysis systems, continuous peritoneal dialysis and ECMO circuits and cardiopulmonary bypass circuits in the cardiac theatre all may contain DEHP.[7]

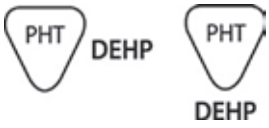
Given the relatively small size of a neonate to the size of the medical devices it is not surprising that the highest levels of urinary MEHP have been measured amongst neonates in Neonatal Intensive Care, and the greater the interventional support the higher the urinary excretion of MEHP.[9] DEHP exposures in NICUs are potentially at or above levels known to cause adverse health effects in animal studies.[10]

The regulatory view

In 2007 the EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) addressed the issue of the toxicity of plasticisers on neonates and other groups possibly at risk in the light of the available evidence from animal studies.[7] The high risk groups included, neonates and preterm males, those requiring exchange neonatal transfusion or receiving TPN as well as pregnant mothers on haemodialysis and adults receiving massive transfusion. SCENIHR could not directly implicate any plasticiser with harmful human effects, but concluded that there was sufficient concern regarding the health effects of DEHP to recommend that it should be substituted with other plasticisers so long as functionality was maintained. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) took the counter view and, given the lack of proven evidence linking DHEP to adverse male reproductive health, concluded that it would be premature to recommend a change to other plasticisers. The MHRA state that the use of a device, in which the anticipated benefits (for example of a DEHP-PVC TPN feeding line) outweigh the potential risk from exposure to DEHP, is acceptable and within the terms of the EU Medical Devices Directive.[11]

Given the European concern over phthalates and DEHP in particular, the amended Medical Device Directive 2007/47/EC introduced compulsory labelling from March 2010 indicating the inclusion of a phthalate (PHT) and specifically which one[12] (Figure 3).

Figure 3
These symbol arrangements indicate the inclusion of the phthalate DEHP within the packaged product



The future and safer plasticisers

The European Parliament continues to be pressurised to work towards a complete ban of DEHP in medical devices.[13]

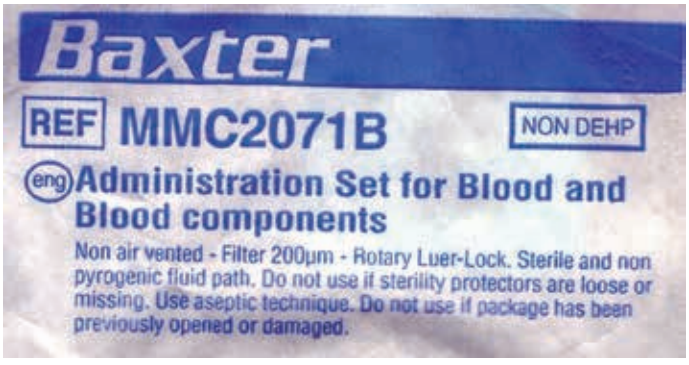
The toxicity depends on the plasticiser, the capacity to leach and the particular organ system. If EU concern equates with toxicity then DBT, DEHP, and BBT are potentially most toxic and DNOP (di-n-octyl phthalate), DINP, DIDP intermediately toxic. The plasticiser Tris (2-Ethylhexyl) Trimellitate (TOTM) is not a phthalate at all, leaches least and is least toxic. It is produced in much smaller quantities worldwide and is more expensive than DHEP. Medical device manufacturers will continue to develop newer, less leaching plasticisers in order to maintain functionality of the device in a PVC market without DEHP.

Medical device choice

There is great pressure to reduce procurement costs, and inevitably PVC devices containing DEHP are cheaper than devices containing purportedly safer, newer plasticisers (see Figures 4 and 5). We believe it is of vital importance to scrutinise the labelling and the nature of the plasticiser when considering the device and the patient for whom that device will be used, before any consideration of the relative cost and performance.

Figure 4
The packaging from a DEHP containing blood giving set. The precautions specifically warn of the hazards of endocrine disruption with prolonged use in infants children and pregnant women

Figure 5
The packaging from a PVC blood administration set that does not contain DEHP indicated by NON DEHP



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