Commentary

The toxicological quandary in the use of plasticizers in medical devices

The introduction of flexible PVC bags for the storage of blood and its components totally replaced the use of glass bottles because of its numerous advantages. Blood bags enable better separation of blood components in a more sterile manner and safer transfusion of components. This has led to increasingly wider use of blood component therapy than whole blood use, thus enabling more effective use of the scarce donor blood that is available. Incidences of reported toxic problems resulting from plasticizer migration during transfusions are rare.

Flexible Poly (vinyl chloride) (PVC) formulations find wide applications in skin contact, food contact and medical devices. Medical devices that may contain di-(2-ethylhexyl) phthalate (DEHP)-plasticized PVC include intravenous (IV) bags and tubing, umbilical artery catheters, blood bags and infusion tubing, nutrition feeding bags, nasogastric tubes, peritoneal dialysis bags and tubing, tubing used in cardiopulmonary bypass (CPB) procedures, in extracorporeal membrane oxygenation (ECMO) and for haemodialysis.

Plasticizer migration from PVC medical devices has been an area of concern for the last few decades that also attracted the attention of numerous investigators due to the large consumption of the polymer in its plasticized form. As unplasticized PVC is generally hard and brittle, addition of this low molecular weight additive facilitates processing operations such as sheet and tube extrusion and injection moulding. The plasticizer molecules separate the PVC chains to allow them to move over one another and thus enhancing the material flexibility. Typical plasticizers for PVC are long chain organic compounds such as phthalates, adipates and organophosphates. Secondary plasticizers include chlorinated paraffins and epoxidised natural oils. However, the most common plasticizer used in PVC medical devices is DEHP, otherwise popularly known as dioctyl phthalate (DOP), particularly because of its non-toxic nature, high versatility and low cost. DEHP is an unusual industrial chemical as it contains only small traces of byproducts. It is also widely employed in food contact applications along with di-2-ethylhexyl adipate (DEHA).

These compounds possess high mobility and are known to migrate from the plastics into the surrounding medium or environment such as food or blood. Previous investigations have shown that patients subjected to chronic dialysis procedures or transfusions receive a certain amount of the plasticizer along with the blood which was retained by the tissues. Considerable amount of work has been done to assess the toxic effects of the plasticizer on the human body. National Institute of Environmental Health Sciences, USA organized several international symposia on phthalate acid esters which reviewed many aspects of these substances including their metabolism, toxicity and methods for their detection in the environment and biological materials.

Currently DEHP continues to be the plasticizer of choice. The EC Scientific Committee on Food (SCF) has concluded that DEHP is not genotoxic and has assigned a tolerable daily intake value of 25 mg/kg body weight. International specifications such as ISO 3826 - 1993 have prescribed in vitro test procedures for estimating the amount of extractable DEHP from blood bag systems. The current limit has been fixed at <10 mg/dl. All currently available PVC flexible medical devices containing plasticizers are subjected to these in vitro tests to ensure that they meet the prescribed limits before they are marketed. In addition, exhaustive animal studies have shown that DEHP does not irritate the skin or mucous membranes. DEHP is estimated to have an LD$_{50}$ value nearer to 30 g/kg whereas toxicologists consider any material having an LD$_{50}$ value of more than 2g/kg as not harmful. Canadian Red Cross has reported that blood stored in flexible blood bags had a longer storage life than that stored in glass bottles and also enhanced in vitro stability of red cells stored in plastic bags containing DEHP. On July 12, 2002 US FDA issued a public health notification stating that there is little or no risk posed by patient exposure to the negligible amounts of DEHP released from PVC intravenous bags.
during the infusion of crystalloid fluids (e.g., normal saline, D5W, Ringer's lactate). Further, there is little risk posed by exposure to the amount of DEHP released from PVC bags used to store and administer drugs that require a pharmaceutical vehicle for solubilization, when label instructions are followed.

Attempts have been made in many laboratories to reduce the migration of plasticizers in two directions. Earlier attempts were to seek an alternate plasticizer to DEHP which is likely to impart optimum properties to PVC. Compounds such as citric acid esters and high molecular weight trimellitates have been used as alternate plasticizers. However, their success on an industrial level has been limited. Subsequent attempts were made to reduce the migration of DEHP by modifying the base polymer by radiation or chemical grafting using various monomers. Scientists at Sree Chitra Tirunal Institute for Medical Sciences & Technology at Thiruvananthapuram, Kerala who were instrumental in development and commercialization of various medical devices including blood bags for the first time in India have also standardized certain methods for reducing the amount of plasticizer migrating into blood and blood products.

Procedures which pose the highest risk of exposure to DEHP include exchange transfusion in neonates, ECMO in neonates, total parenteral nutrition (TPN) in neonates (with lipids in PVC bag), multiple procedures in sick neonates (high cumulative exposure), haemodialysis in peripubertal males, haemodialysis in pregnant or lactating women, enteral nutrition in neonates and adults, heart transplantation or coronary artery bypass graft surgery (aggregate dose), massive infusion of blood into trauma patient and transfusion in adults undergoing ECMO. In short, greatest concern would be for very young male infants who are critically ill and have prolonged exposure to multiple devices containing DEHP. Also at risk would be the male foetus, through exposure of his mother, and peripubertal males. In contrast, there is little concern for adults receiving intravenous solutions or undergoing peritoneal dialysis. For some of the above procedures, PVC devices that do not contain DEHP can be substituted, or devices made of other materials can be used, if available. If PVC devices containing DEHP must be used, one may be able to minimize exposure to DEHP by using the blood products stored for the shortest duration at the lowest possible temperature, or by using heparin-coated ECMO circuits. For other patient groups, presumably at lower risk, the decision to use DEHP alternatives must take into account the medical advantages and drawbacks of the substitute materials and their availability.

One of the best safety assessments was carried out by the US FDA due to serious concerns expressed in various forums and the document, "Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices," can be found on the US FDA's CDRH web site at www.fda.gov/cdrh/ost/dehp-pvc.pdf. European Pharmacopoeia together with German and British health authorities have recommended only DEHP for use in flexible PVC for blood and intravenous fluid containers and tubing.

In this issue, Gayathri et al discuss the hormonal changes caused by low doses of DEHP and the resultant toxic effects observed in rats. This paper assumes importance especially in the changing scenario of global concern on health and standards of human life. The authors have concluded, like many others before them, that it is necessary to reduce the plasticizer migration levels. But this seems to remain an idealistic objective. In spite of the best efforts by numerous research groups around the world, a better alternative plasticizer to DEHP or a better material to replace plasticized PVC is yet to be found and accepted by the medical and industrial community. And that probably is a great challenge to the inveterate inventor.

V. Kalliyana Krishnan & G.S. Bhuvaneshwar
Biomedical Technology Wing
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram, India

References


6. FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP, July 12, 2002, Maryland, USA.


9. European Pharmacopoeia Section VI.1.2.1. 2nd ed. Materials based on PVC.

10. DEHP. In: Medizinischen Gegenstanden aus Kunstoffe [PVC], February 1989, Bundesgesundheitsblatt, Germany.