

## Original Articles

# The Effect of Priming Solutions and Storage Time on Plasticizer Migration in Different PVC Tubing Types—Implications for Wet Storage of ECMO Systems

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**Abstract:** The wet priming of extracorporeal membrane oxygenation systems and storage of these systems for rapid deployment is common practice in many clinical centers. This storage policy is, however, seen by many to be controversial due to the potential adverse effects associated with the migration of the di(2-ethylhexyl) phthalate plasticizer (DEHP) from the polyvinyl chloride (PVC) circuit tubing and issues surrounding the maintenance of sterility. This study was performed to evaluate the effects of both short and long-term storage and priming fluid type on plasticizer migration from four commonly used PVC tubes in extracorporeal membrane oxygenation therapy circuits. The four tubes incorporating three plasticizers, two DEHP, one tri(2-ethylhexyl) trimellitate (TOTM), and one dioctyl adipate (DOA) were exposed to each of the three priming fluids for a period of 28 days. Samples were taken at time intervals of 1, 4, 8, 24, and 48 hours, followed by samples at 7, 14, and 28 days. Each sample was processed using a spectrophotometer and the concentration of plasticizer leaching

into each solution at each time-point determined. There was a time dependent increase in plasticizer leached from each tube. The migration was greatly affected by both the priming fluid and tubing type. The migration of DEHP was higher than that of TOTM and DOA over both the short and long-term exposure levels. Plasticizer migration occurs from all of the tubes tested over the long term. The TOTM and DOA tubes performed better than the DEHP counterparts in the short term. Selection of priming fluid has a major bearing on plasticizer migration with significant lipid and protein containing fluids promoting higher migration than simple sodium chloride .9% solution prime. The results suggest that DOA tubing and sodium chloride .9% solution priming fluid should be selected if wet primed perfusion circuits are to be used over short terms of storage. **Keywords:** di(2-ethylhexyl) phthalate, extracorporeal membrane oxygenation therapy, migration, plasticizer, storage. *JECT. 2009;41:199–205*

di(2-ethylhexyl) phthalate (DEHP) is the most commonly used plasticizer for medical grade polyvinyl chloride (PVC). It is used primarily to impart flexibility into what would otherwise be a ridged polymer and can represent up to 40% of the total polymer weight. The excellent physical properties and versatility of plasticised polyvinyl chloride (P-PVC) have made it one of the most commonly utilized polymers in clinical practice. DEHP itself is not covalently bonded to PVC resin, it is therefore mobile within the blend and has the potential to migrate from the

plastic when exposed to blood, serum, or some pharmaceutical products. Hence, patients undergoing a variety of procedures such as blood transfusions, nutritional support, intravenous therapy, cardiopulmonary bypass (CPB), and extracorporeal membrane oxygenation therapy (ECMO) are exposed to a varying amount of P-PVC and in turn the mobilized or leached DEHP.

Previous studies have shown that DEHP and its metabolites have been identified in blood products (1–4) and tissues (5,6) as well as intravenous solutions (7) and pharmaceuticals (8,9). As a result of these findings, potential toxic effects of DEHP have been the focus of considerable research effort for some time. Much of this work has been carried out using animal models of various clinical interventions. These studies have given rise to some concern, in particular, the confirmation that DEHP is both a potential carcinogen and a toxic agent (10), particularly with

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regard to the reproductive systems in male rodent species. More recently, DEHP has been shown in both rodents and humans to be a significant inflammatory mediator (11–14), and this trait has prompted concern in the clinical CPB and ECMO arenas, especially regarding the potential scope for inflammatory mediated complications during and post procedures. Various regulatory bodies have responded to these issues, and have reported on DEHP and its use in medical devices. These bodies have concluded that critically ill neonates and those patients who undergo chronic procedures, such as hemodialysis and multiple blood transfusions, are the most at risk from the adverse effects from DEHP exposure (15–18).

Despite these well-described issues, DEHP continues to be the most widely used plasticizer in medical practice. There are a number of reasons for this, but low cost and the very good mechanical properties associated with DEHP use are certainly two of these. However, bearing in mind the potential for adverse effects associated with the deployment of DEHP, there are a number of clinical interventions in which there may be real cause for concern. Principal amongst these are the various extracorporeal applications, hemodialysis, CPB, and in particular ECMO where the PVC surface area to body mass relationship and duration of exposure is at its most extreme. The knowledge of the possible adverse effects of DEHP has led many manufacturers in this field to investigate possible alternative plasticizers and other means of reducing the migration of the DEHP plasticizer from PVC tubing. Several approaches to this have evolved over the years including the use of elaborate surface modification and coating technologies (19) and the incorporation of more biocompatible molecules like Heparin into the plastic structure (20). These techniques have been shown to reduce the levels of DEHP migration into test solutions, but they have been only sporadically adopted by the clinical setting, as they increase the cost of the tubing material and the evidence for DEHP mediated complications has not been truly clinically defined.

As health providers around the world express an interest in alternatives to DEHP plasticized PVC, the commercial sector has been investigating alternatives, for example tri(2-ethylhexyl)trimellitate (TOTM) and dioctyladipate (DOA), both of which are more expensive than DEHP, but exhibit much lower migration levels and impart similar mechanical properties of DEHP plasticized PVC. These alternatives are very promising, but the cost/benefit balance associated with their deployment needs to be fully elucidated before they will be widely used. However, there are niche sectors of clinical practice in which these materials are already being deployed, and these include the high-risk groups highlighted by the regulatory bodies, including neonatal ECMO patients. It must be stressed however, that although the migration rate of these new plasticizers is lower than

that of DEHP, their toxicology profile, particularly in blood contacting environments, is not, at present, well described.

In response to the need for a more comprehensive understanding of the possible exposure of patients to plasticizers that are used regularly in ECMO, this study has been designed to investigate one particular issue associated with plasticizer migration; the effect of wet storage of ECMO circuits, a fairly common clinical practice, on the migration of plasticizers. In addition we investigated the effect of the makeup of the priming solutions and different plasticizer types used on plasticizer migration under long-term storage conditions.

Whether it is appropriate to store primed ECMO circuits for future use has been a matter of debate for some time, and the focus of this clinical debate has tended to revolve around possible infection issues, and effects on oxygenator performance. Our study, carried out under laboratory conditions, aims to determine the levels of plasticizer exposure presented by wet storage of various ECMO tubing types and priming solutions. The potential clinical impact of DEHP exposure remains controversial, however, there is a body of literature that suggests such exposure is undesirable in the clinical setting.

## METHODS AND MATERIALS

The experiments were conducted in the laboratories in the bioengineering unit at the University of Strathclyde, and materials used in the experiments were kindly provided by the perfusion staff at the Yorkhill Children's Hospital in Glasgow. The study involved the testing of the four most commonly used tubing types that are found in ECMO circuits within the National Health Service Scotland and exposing them to three common priming solutions. The investigators were blinded to the tubing type and priming fluids used, both of which were supplied unmarked by the clinical partners. The tubing was labeled A, B, C, and D and the priming solutions numbered 1, 2, and 3. Only at the end of the experiment were the names and manufacturers of the tubing and fluids revealed to the investigators. These designations relate to the following materials:

Fluid 1: .9% Sodium Chloride Solution

Fluid 2: 2/3 .9% Sodium Chloride Solution and 1/3 20% Human Albumin

Fluid 3: 2/3 Gelofusine and 1/3 Hartmann's Solution

Tube A: EEC Blood Line. Raumedic, Munchberg, Germany.

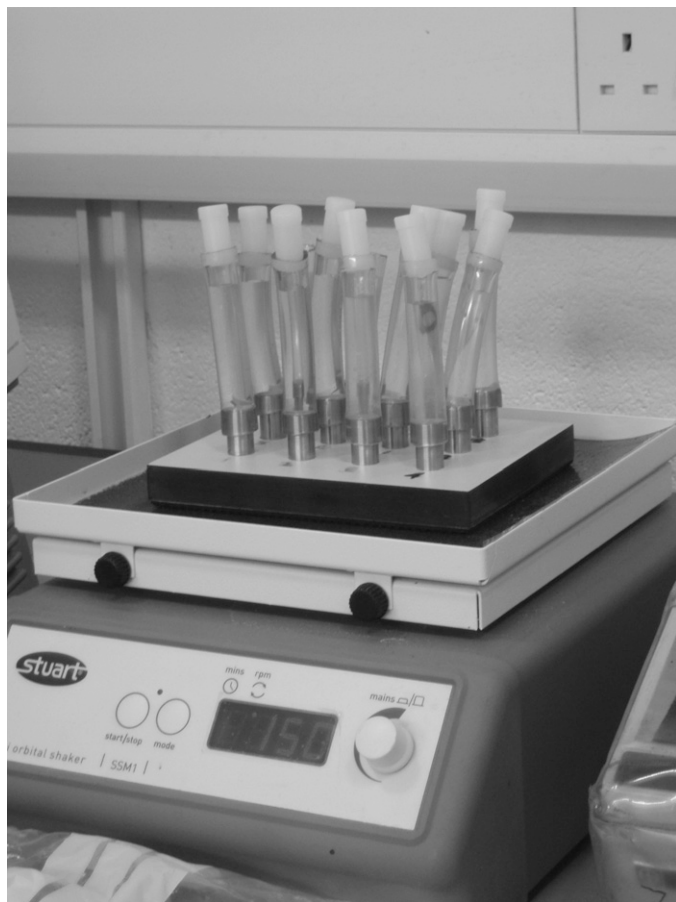
Tube B: Dideco XS. Sorin Group, Arvada, CO.

Tube C: Action. Tekni-plex, Somerville, NJ.

Tube D: Tygon S95-E. Saint-Gobain, Akron, OH.

### Experimental Setup

Three 8 cm sections of each tube type was cut and placed on a test rig (Figure 1). Five centimeters of this tube were



**Figure 1.** Experiment test rig set up showing the constrained and sealed tubes on the tubing block positioned on an orbital shaker.

then exposed to each of the test fluids and a nonplasticized polyurethane stopper was then applied to the open end of the tube. The test rig was then placed on an orbital shaker plate at 150 rev/min to simulate gentle recirculation, a common clinical practice.

Samples of the test solutions were taken at 0 hours, 1 hour, 4 hours, 8 hours, 24 hours, 48 hours, 7 days, 14 days, and 28 days. The plasticizer content of each sample was measured using a spectrophotometer (Ultrospec 4300pro, GE Healthcare Lifesciences, Piscataway, NJ) over a wavelength range of 200–900 nm, running a Wavescan analysis program. The samples were then returned to the tubes after the reading had been taken. The reference sample used for all sample readings was a 100% sodium chloride .9% solution. A concentration curve for all plasticizers was also plotted using known concentrations, DOA, and TOTM suspended in methanol, and this was used for calculating plasticizer concentrations.

### Concentration Analysis

The concentration of plasticizer present in the test samples, which represents the plasticizer migration level, was determined by measuring the appropriate peak absorbance

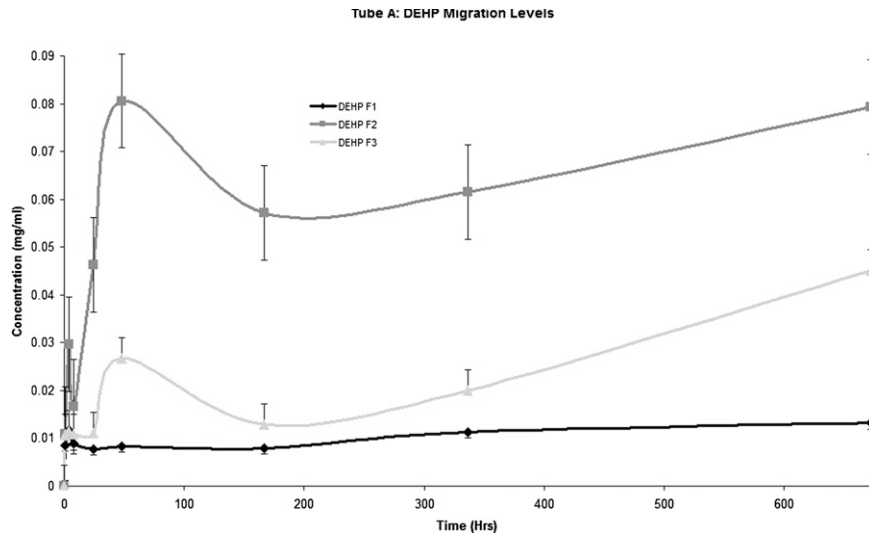
height. This value was then translated into a concentration by referring to the concentration curves plotted previously. This technique had been used successfully in previously published works by Gourlay et al. (14) and also by Zhao and Courtney (21).

### Statistical Methods

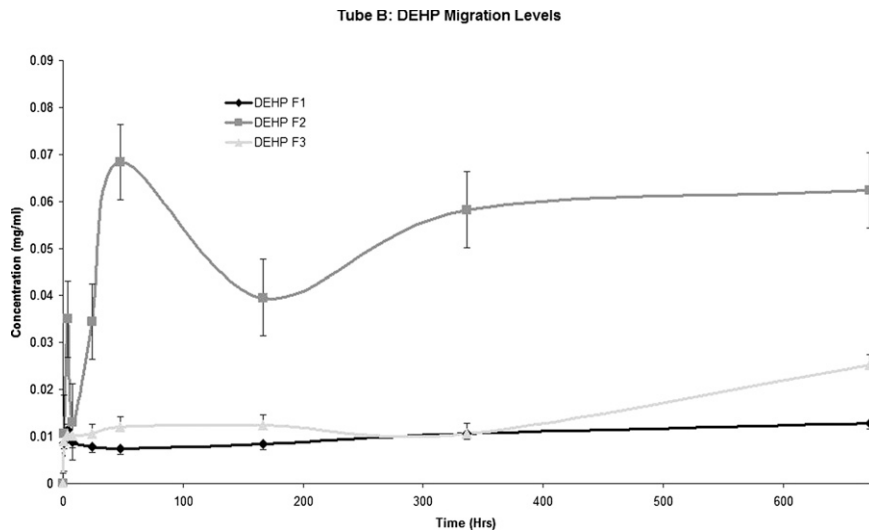
The statistical analysis in this study was performed using the MiniTab V15 statistical software tool (Minitab Ltd. Coventry, United Kingdom). Using this software, descriptive statistics were used to calculate the mean and standard deviations of the samples. The probability values quoted in this paper manuscript were also determined by performing a *t*-Test using the same software package.

## RESULTS

The results from the recirculation migration experiments for Tubes A, B, C, and D are shown in Figures 2–5. The results clearly demonstrate that in all tubing types, in the presence of all fluids, there was evidence of plasticizer migration. The level of migration, however varied significantly over time and in response to fluid type. The DEHP migration profiles for both DEHP plasticized tubing types were fairly similar. Detectable levels of plasticizer migration were seen after as little as 1 hour of exposure to the test fluids in both cases. Fluid 1 (sodium chloride .9% solution) was associated with the lowest level DEHP migration from the tubing with levels that varied between  $.0079 \pm .00031$  mg/mL, and  $.008 \pm .00031$  mg/mL out to 7 days of exposure. The concentration levels tended to increase consistently from 14–28 days of exposure with a final value of  $.0132 \pm .0022$  mg/mL and  $.0128 \pm .0043$  mg/mL for tubes A and B respectively, although this difference was not statistically significant ( $p > .05$ ). In terms of DEHP migration, Fluid 3 was associated with a similar migration profile as seen with the sodium chloride .9% solution. However, the overall DEHP concentrations were generally higher at around  $.0128 \pm .00082$  mg/mL to  $.0125 \pm .000793$  mg/mL at 7 days of exposure for tubes A and B. This difference in concentration was statistically significant in both cases,  $p < .01$  and  $p < .01$  respectively when comparing tubing types with respective fluid compositions. After 7 days, Tube A seemed to leech greater amounts of plasticizer than Tube B, with concentration levels of  $.019 \pm .0072$  mg/mL and  $.0451 \pm .019$  mg/mL after 14 and 28 days respectively compared to  $.011 \pm .0024$  mg/mL and  $.0252 \pm .0156$  mg/mL for Tube B. These differences were statistically significant at both 14 and 28 days,  $p < .03$  and  $p < .04$  respectively. In addition the differences in leaching rate at the 14 and 28 day exposure levels differed significantly between common tubing types, but with different priming solutions. Once again the plasticizer levels associated with Fluid 3 (Gelofusine and 1/3 Hartmann's solution) were significantly higher than that



**Figure 2.** Graph of DEHP concentration levels migrated from Tube A in mg/mL.



**Figure 3.** Graph of DEHP concentration levels migrated from Tube B in mg/mL.

of sodium chloride .9% solution alone ( $p < .045$  for Tube A and  $p < .049$  for Tube B).

Fluid 2 (.9% sodium chloride solution and 1/3 20% human albumin) was associated with the highest level of DEHP migration into the priming fluid when compared to the other solutions. The migration profile over the first few hours was seen to follow a parabolic shape but after 8 hours (Figures 1 and 2) and out to 28 days followed more of a linear pattern. The concentration levels at 24 hours reached  $.0464 \pm .027$  mg/mL and this continued to increase linearly to  $.079 \pm .025$  mg/mL and  $.0624 \pm .0134$  mg/mL after 28 days for Tubes A and B respectively. This was statistically significantly higher than the other priming solutions used ( $p < .039$ , and  $p < .007$  when comparing Tube A and B with Fluids 2 and 3 respectively).

The TOTM plasticized tube, Tube C was associated with a much lower migration rate than the DEHP plasticized tubes. Of particular interest was the finding that this slow migration rate was consistent with all fluid types. Fluids 1 and 3 exhibited a low level of extraction over the entire 28-day test period. Indeed the concentration levels were  $.0086 \pm .00057$  mg/mL and  $.0067 \pm .0023$  mg/mL for Fluids 1 and 3 respectively at 28 days, around 10% of the levels observed at this time-point with the DEHP tubes. Only Fluid 2 (.9% sodium chloride solution and 1/3 20% human albumin) showed any significant increase in migration of the plasticizer with the TOTM plasticized tube, but this occurred only after 14 days of exposure and remained fairly constant out to 28 days, at a level only slightly, and not significantly, higher than that seen with Fluids 1 and 3.

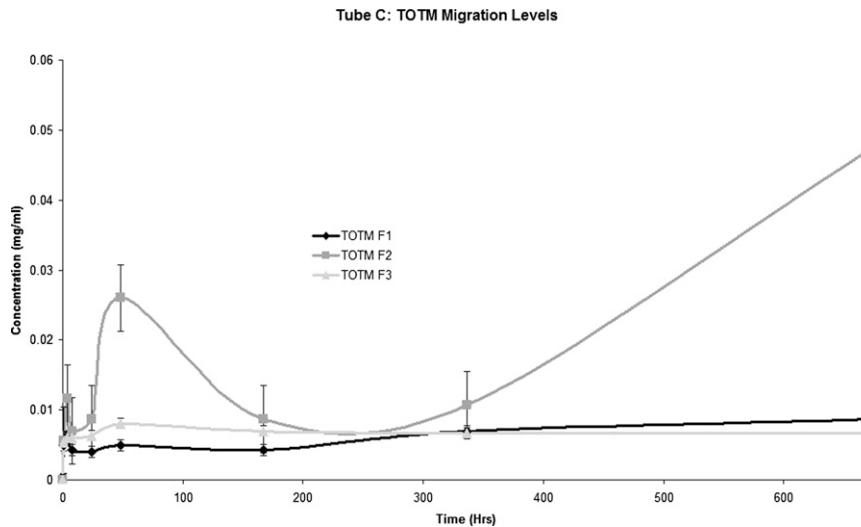


Figure 4. Graph of the migration concentration levels over the entire test period for Tube C in mg/mL.

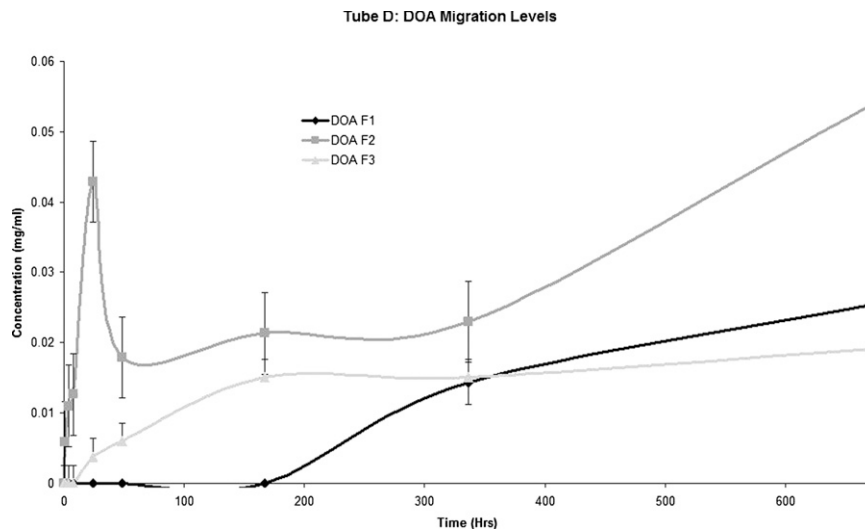


Figure 5. Graph showing the migration concentration levels over the entire test period for Tube D in mg/mL.

The DOA plasticized tubing, Tube D, exhibited no measurable migration over the first 4 hours in any of the test fluids. This trend continues for both Fluids 1 and 3 out to 8 hours and in the case of Fluid 1 it continues right out to 7 days. For Fluid 1, concentration levels at 14 days were seen to be around  $.0143 \pm .012$  mg/mL and this steadily increased to around  $.0252 \pm .02$  mg/mL at 28 days. Fluid 3 followed a similar pattern to Fluid 1 with no plasticizer migration being detected in the first 8 hours. The concentration levels were then seen to increase after 24 hours of exposure and further increased at a steady rate out to  $.019 \pm .016$  mg/mL after 28 days.

In common with the DEHP experiments, Fluid 2 (.9% sodium chloride solution and 1/3 20% human albumin) was associated with the highest level of DOA migration

with detectable levels after only 8 hours. This level then steadily increased in a near-linear fashion from 48 hours out to 28 days where a final concentration in the sample was determined as  $.054 \pm .047$  mg/mL, the highest level detected in this study.

**DISCUSSION**

This study has shown quite clearly that plasticizers, utilized in the tubing element of perfusion circuits, migrate into the priming fluid. This is the case for all plasticizers investigated in the present study. However, there are clear differences in terms of the migration rate and the time-frame of migration between the tubing types. The study

suggests that the concentration of plasticizer observed in the priming solution depends upon three factors:

1. The plasticizer type
2. The priming fluid
3. Storage time

In general DEHP was seen to readily migrate into all of the priming solutions. The two alternative plasticizers both exhibited a marked reduction in migration compared to the DEHP over the entire time period, and performed much better over the shorter time period out to 48 hours and the concentration levels only started to increase after 14–28 days (Figures 4 and 5). The extremes of the time-scale studied in the present study are probably not reflective of clinical practice, but the shorter term exposure levels, out to the 7 day level are within the margins of clinical practice. Critically, the early phase of this study is similar to that seen in previous studies, where DEHP plasticized tubing was exposed to migration media. Gotardo and Monteiro (8) reported a very similar profile, with the exception that they recorded little migration in the first 3 hours. We, on the other hand, did see migration of DEHP into all media from the very outset. One possible explanation for this is the fact that we did not prewash our circuits and under these circumstances (which are similar to the clinical setting) one might anticipate a surge of DEHP from the surface of the tubing, followed by a slower emission. This precisely describes the profile we observed. The findings of this study are corroborated by the findings of studies by both Karle et al. (22) and Burkhart et al. (23) as they also reported the detection of significant levels of migrated DEHP into whole blood and a high protein content priming fluid. In the case of Karle et al. (22) they reported that exposure to migrated DEHP can be as much as 20–70 times higher in ECMO than other procedures such as transfusions and dialysis. Furthermore, it is clear that the level of DEHP migration is effected by the priming fluid into which it comes into contact. The albumin and Gelofusine solutions, which contain both lipid and protein components, were associated with greater migration rates. Whilst these studies show that DEHP migrates from the PVC used in clinical procedures, there are a number of studies that reported no accumulation of DEHP during storage experiments. The migration of DEHP from PVC is known to happen constantly from the bulk of the material to the material surface. Therefore, the findings of these studies by Han et al. (24) and Riley et al. (25) have to be questioned as to why they found no DEHP. This may well be related to the sensitivity of the detection methodology, given that the levels being detected are fairly small.

Our study confirms that there is a much lower migration rate from the alternative plasticizers TOTM and DOA. This was particularly clear during the early phase of the study where DOA was associated with virtually no migration

for up to 7 days of exposure to sodium chloride .9% solution. That DOA and TOTM moderate plasticizer migration confirms the information from the manufacturers of these materials, who market the tubes as low- or nonmigration PVC tubing.

Resistance to migration is not the only factor in deciding if these tube types are a better proposition than DEHP Plasticized PVC in the clinical setting. Cost and toxicity are also factors. Currently, both alternatives are more expensive than the DEHP option and their toxicological profiles are not as yet fully described. Further studies therefore are required to establish if using these materials is subjecting patients to a low dose of a more toxic substance than DEHP. However, assuming that the toxicity profile of these molecules is similar to DEHP, and that our previous studies have shown that the inflammatory response to DEHP is dose dependent, the use of these low leaching plasticizers may offer some form of inflammatory benefit.

The second major finding, not entirely unexpected, was that the makeup of the priming solution has an impact on the level of plasticizer migration. This is not surprising as we know for example that DEHP and, indeed, the other plasticizers involved in this study are to some extent lipophilic. These are complex molecules with complex chemical properties, which might affect migration tendency. In this study, it was clear that the simple sodium chloride .9% solution priming solution was associated with the lowest level of migration from all tubing types over the entire timecourse of the study. The more complex priming solutions were associated with the highest migration rates. The high lipid solutions, those containing albumin, and the gel-fusine had the highest migration rates, possibly highlighting some of the complex affinities of the plasticizer molecules, which have not been investigated in this study. The presence of the albumin in solution was associated with the highest migration rates, and its use in wet prep circuits should be applied with caution, as it seems to promote excessive migration of DEHP over short time periods (<48 hours). It also promoted a moderate migration response in the other plasticizers, but only at long-term storage times of 14 days plus.

## LIMITATIONS

The main limitation of this study is the fact that we utilized fairly small sections of tubing material; this resulted in small but significant levels of leached plasticizer. A larger surface area with smaller priming volume may well have amplified the results. However, we were keen to use only clinically relevant materials and designed the test system and protocols to use these. The detection limitation of the spectrophotometer system was initially considered to be a

concern, however, previous studies and this current study confirm that the levels detected are well within the limitations of the technology.

## CONCLUSION

It was clear from this study that plasticizers migrate from PVC tubes at different rates depending on the time-course and the makeup of the priming solutions. This study would suggest that if wet-storage of the perfusion circuits is to be used, then DOA plasticized tubing combined with a simple sodium chloride .9% solution priming solution offers the best protection from the toxic effects of migratory plasticizers.

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