Chemosphere 145 (2016) 10–16

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Comparative study on the migration of di-2-ethylhexyl phthalate (DEHP) and tri-2-ethylhexyl trimellitate (TOTM) into blood from PVC tubing material of a heart-lung machine

Elisabeth Eckert [b, *], Frank Münch [a], Thomas Göen [b], Ariawan Purbojo [a], Johannes Müller [b], Robert Cesnjevar [a]

[a] Department of Pediatric Cardiac Surgery, University Hospital Erlangen, Loschgestr. 15, Erlangen 91054, Germany
[b] Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Schillerstrasse 25/29, Erlangen, 91054 Germany

HIGHLIGHTS

- Comparative migration study using PVC blood tubing plasticized with TOTM and DEHP.
- Determination of TOTM degradation products in blood for the first time.
- TOTM degradation products represent a major share of total TOTM migration in blood.
- The plasticizer TOTM does possess a significantly lower leachability than DEHP.
- Storage time of blood tubing material has considerable influence on migration rate.

ARTICLE INFO

Article history:
Received 26 August 2015
Received in revised form
10 November 2015
Accepted 19 November 2015
Available online xxx

Handling editor: A. Gies

Keywords:
Plasticizers
Blood tubing
Silicone
Medical devices
PVC
Leaching

ABSTRACT

Medical devices like blood tubing often consist of PVC material that requires the addition of plasticizers. These plasticizers may migrate into the blood leading to an exposure of the patients. In this study the migration behavior of three different blood tubing sets (PVC material with two different plasticizers and silicone as control material) applied on a heart-lung machine standardly used for cardiopulmonary bypass (CPB) in children was studied. We analyzed the total plasticizer migration by analysis of both, the parent compounds as well as their primary degradation products in blood. Additionally, the total mass loss of the tubing over perfusion time was examined. The PVC tubing plasticized with DEHP (di-2-ethylhexyl phthalate) was found to have the highest mass loss over time and showed a high plasticizer migration rate. In comparison, the migration of TOTM (tri-2-ethylhexyl trimellitate) and its primary degradation products was found to be distinctly lower (by a factor of approx. 350). Moreover, it was observed that the storage time of the tubing affects the plasticizer migration rates. In conclusion, the DEHP substitute TOTM promises to be an effective alternative plasticizer for PVC medical devices particularly regarding the decreased migration rate during medical procedures.

1. Introduction

Medical devices often consist of PVC (polyvinyl chloride) material that requires the use of plasticizers. The plasticizer concentration in PVC medical devices generally ranges between 20 and 40% of the total weight formulation [IARC 2012; Bernard et al., 2015; Council of Europe (2014)]. Plasticizers are not chemically bound to the PVC material and may thus easily migrate. Patients undergoing certain medical procedures as blood transfusion, hemodialysis or cardiopulmonary bypass (CPB) may thus be significantly exposed to these plasticizers. The most prominent plasticizers for PVC material are phthalic acid diesters (phthalates) with DEHP (di-2-ethylhexyl phthalate) as the main commonly used representative. Several studies demonstrated that DEHP leaches

* Corresponding author
E-mail addresses: elisabeth.eckert@fau.de (E. Eckert), Frank.Muench@uk-erlangen.de (F. Münch), Thomas.Goeen@fau.de (T. Göen), Ariawan.Purbojo@uk-erlangen.de (A. Purbojo), Johannes.Mueller@ipasum.med.uni-erlangen.de (J. Müller), Robert.Cesnjevar@uk-erlangen.de (R. Cesnjevar).

http://dx.doi.org/10.1016/j.chemosphere.2015.11.067
0045-6535/

from PVC medical devices into blood products and thus into patients undergoing transfusions or maintenance hemodialysis [Kambia et al., 2001; Pollack et al., 1985; Inoue et al., 2005]. Severe toxicological concerns exist regarding adverse developmental and reproductive effects of DEHP and other phthalates [Tickner et al., 2001; Heudorf et al., 2007]. DEHP itself is classified as a Category 1B with the hazard notation H360 (former EU classification 2): "reproductive toxicant for both fertility and developmental effects". Furthermore, it is classified as possibly carcinogenic to humans [IARC 2012]. That resulted in a ban of DEHP and some other phthalates in toys and childcare articles by the European Union [Directive 2005/84/EC]. In medical products, however, DEHP is still in use, even for the treatment of vulnerable individuals as pregnant women, neonates and infants in general. Although, the overall benefit of these medical procedures may overweight the risks regarding the elevated DEHP exposure, the question arises whether alternative plasticizers or plasticizer-free material should be applied for medical procedures particularly in pediatrics [Simmchen et al., 2012].

Alternative materials are polyolefines or silicones that do not require the use of plasticizers. Another approach is the use of PVC with alternative plasticizers. Currently, there are several DEHP alternatives for use in medical devices. The most important are diisononyl cyclohexane-1,2-dicarbonylate (DINCH), di-2-ethylhexyl terephthalate (DEHT) as well as adipates and citrates [Bernard et al., 2015]. Another one is tri-2-ethylhexyl trimellitate (TOTM or TEHTM) that is increasingly used as DEHP substitute in medical applications [Van Vliet et al., 2011]. Almost all DEHP substitutes possess a significantly lower toxic potential than DEHP (as reviewed by Bui et al., 2016) although in many cases the toxicological data is rather limited. Initial studies also suggest that TOTM exhibits a lower toxicity compared to DEHP [Bui et al., 2016; Chiellini et al., 2013; Ohashi et al., 2005; Kambia et al., 2004]. Moreover, TOTM is supposed to show a significantly higher degree of stability associated with a decreased migration rate in blood or other liquids [Bernard et al., 2015; Bui et al., 2016]. However, up to now there is still little data on TOTM exposure, toxicity and leachability from medical devices [Kambia et al., 2001; Bui et al. 2016; Kambia et al., 2004; Ito et al., 2008].

In order to evaluate the exposure situation concerning plasticizers in medical devices several analytical approaches are possible. One is the determination of the plasticizer concentration in the medical devices itself. For this purpose, a number of different analytical methods are available (reviewed by Bernard et al., 2015). Another approach is to determine the plasticizer concentration that migrated from the medical device. Therefore, it is possible to analyze the plasticizer leachability using migration experiments into simulants or to examine the inner exposition of humans by analysis of the plasticizers and/or its metabolites in biological material. Many analytical methods are available for the determination of DEHP and its major metabolites [Pollack et al., 1985; Inoue et al., 2005; Silva et al., 2006]. For TOTM and its metabolites, however, analytical methods are rarely available (reviewed by Eckert et al., 2015). Recently, an analytical method was published that enables for the first time the specific determination of TOTM and its primary degradation products in blood [Eckert et al., 2015].

It was the aim of this study to assess the exposure situation regarding plasticizer migration of patients that have to undergo surgery under application of CPB. Therefore, an in-vitro comparative study was conducted using three different tubing sets that were installed on a heart-lung machine designed for children up to 5 kg body weight (BW). We examined the time-dependent migration rate of the plasticizers, i.e. of the standard plasticizer DEHP and its substitute TOTM over a perfusion time of 24 h. To enable a comprehensive determination of the total plasticizer migration during CPB we included the determination of the primary degradation products of the abovementioned plasticizers in blood. A silicone blood tubing set was used as control material as silicone is often used as an alternative plasticizer-free material. Additionally, the absolute mass loss of the tubing was examined.

2. Experimental

2.1. Material

For this study, three different types of blood tubing sets were used. The blood tubing set of Group 1 consisted of standard PVC material plasticized with DEHP. The tubing of Group 2 comprised the so called "noDOP"-material consisting of PVC plasticized with TOTM. The blood tubing set of Group 3 was made of silicone and was used as control material, as silicone is operable without the use of any plasticizers. The PVC tubing of Group 1 and Group 2 were all uncoated and were provided by Sorin Group (München, Germany) and Raumedic AG (Helmbrechts, Germany), respectively. The silicone tubing set (Group 3) was provided by Sorin Group (München, Germany). The perfusion experiments were carried out separately with six different bloodlines for each tubing set. Four bloodlines each were tested after a storage period of 30 weeks and two of each directly after production (storage time of two weeks).

To avoid potential contamination, special attention was paid to ensure that the packaging of each blood tubing set as well as the syringes for blood sampling were plasticizer-free. Sheep blood was purchased from Fiebig Animalblood Products (Idstein-Niederauroff, Germany) and was stored in glass vials. Likewise, until analysis, the blood samples were stored at −20 °C in glass vials. To achieve a similar composition of the blood solution in comparison to the treatment of a patient of 5 kg BW, 320 mL of sheep blood (containing 16,000 IU heparin sodium) were mixed with the following substances: 15 mL 20% aqueous mannitol (Serag-Wiessner, Naila, Germany), 5 mL 1 M sodium bicarbonate solution (Serag-Wiessner, Naila, Germany), 0.5 mL Konakion® 10 mg/mL (Roche, Grenzach-Whylen, Germany), 2 mL Magnesiocard® 3 M (Verla-Pharm, Tutzing, Germany), 2.5 mL vitamin C 500 mg/5 mL (Rotexmedica, Trittau, Germany), 0.5 mL Cyclokapron® 20 mg/mL (prepared by the pharmacy of the university hospital Erlangen, Germany) and 0.4 mL sodium nitroprusside 60 mg/mL (Adeka, Turkey).

2.2. Instrumentation

The in-vitro tests were carried out using a perfusion system designed for patients up to 5 kg BW (see Fig. 1). For this purpose, the different blood tubing sets were installed on a Stöckert S3 heart-lung machine equipped with a D100 Neonatal Oxygenator (Sorin Group, München, Germany). The Oxygenator was featured with a phosphorylcholine coating (Ph.i.s.i.o®). All pressure measurement lines and the pump segments were plasticizer-free and consisted of polyurethane and silicone, respectively. The contact surface of the blood-carrying tubes was 0.178 m^2; with a priming volume of 237 mL excluding the surface of the Oxygenator and the arterial filter that were also plasticizer-free.

2.3. In-vitro perfusion experiments

Prior to perfusion, a labeled tubing segment with a length of exactly 1 m was taken from each blood tubing set and weighed on an analytical scale (Sartorius, Göttingen, Germany). Subsequently, the blood tubes were installed for perfusion on the heart-lung machine including the labelled tubing segment. The priming of each set was first carried out using 500 mL of Jonosteril® solution (Fresenius Kabi, Bad Homburg, Germany) each with the addition of