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Phthalate and Alternative Plasticizers in indwelling Medical Devices in Pediatric Intensive Care Units

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Highlights:

- A wide variety of chemicals were identified in medical devices from pediatric ICU
- Predominant use of DEHP as plasticizer, followed by DEHA, DEHT and TOTM
- Devices containing TOTM also contained DEHP and DEHT
- Only a small fraction of samples contained unidentified compounds

Abstract

The present study aimed to identify plasticizers present in indwelling plastic medical devices commonly used in the pediatric intensive care unit (PICU). We have analyzed a wide range of medical devices (*n*=97) daily used in the PICUs of two academic hospitals in Belgium and the Netherlands. Identified compounds varied between the samples. Most of the indwelling medical devices and essential accessories were found to actively leach phthalates and alternative plasticizers. Results indicated that DEHP was predominantly present as plasticizer (60 of 97 samples), followed by bis(2-ethylhexyl) adipate (DEHA, 32 of 97), bis(2-ethylhexyl) terephthalate (DEHT, 24 of 97), tris(2-ethylhexyl) trimellitate (TOTM, 20 of 97), and tributyl-O-acetyl citrate (ATBC, 10 of 97). Other plasticizers, such as di-isononyl-cyclohexane-1,2-dicarboxylate (DINCH, 2 of 97), di-isononyl phthalate (DiNP, 4 of 97), di(2-propylheptyl) phthalate (DPHP, 4 of 97) and di-isodecyl phthalate (DiDP, 2 of 97) were detected in < 5% of the investigated samples. Several devices contained multiple plasticizers, e.g. devices containing TOTM contained also DEHP and DEHT. Our data indicate that PICU patients are exposed to a wide range of plasticizers, including the controversial DEHP. Future studies should investigate the exposure to APs in children staying in the PICU and the possible health effects thereof.

Keywords: Medical devices; PICU; DEHP; Phthalates; Alternative Plasticizers

1. Introduction

Pediatric intensive care relies heavily on the use of soft and flexible indwelling medical devices, like intravenous catheters and cannulas, which are indispensable to administer medicines and parenteral feeding to the patient. These devices are mostly made of polyvinyl chloride (PVC), an inherently rigid polymer. To increase flexibility and softness, phthalates, and in particular di(2-ethylhexyl) phthalate (DEHP), have been historically used as plasticizers (or softeners) for plastic indwelling medical devices [1]. They are primarily used to soften devices used in infusion and transfusion, nutrition, and haemodialysis (i.e., infusion or transfusion sets, feeding tubes for enteral and parenteral food administration, and arterio-venous lines). DEHP is not chemically bound to plastics and can thus leach from the medical devices during the use. In critically ill neonates, the urinary levels of DEHP metabolites have been correlated with the number of DEHP-containing medical devices and even exceeded the average daily adult exposure by 1-2 orders of magnitude [2, 3]. Recently, DEHP metabolites have been found at high levels of up to 10 µM in urine and blood of critically ill adults and children following the use of indwelling medical devices [4, 5]. This is worrying as DEHP, and its more active monoester mono (2-ethylhexyl) phthalate (MEHP), exert antiandrogen effects and adverse reproductive and developmental effects, as observed in experimental and preliminary epidemiological studies [6-8]. In addition, a study conducted in the neonatal intensive care unit (NICU) found that the use of infusion systems containing DEHP for administering parenteral nutrition (PN) was associated with a 5.6-fold increase in risk of cholestasis and that the incidence of this hepatobiliary dysfunction declined from 50 to 13% after switching to DEHP-free infusion systems [9].

Due to its carcinogenic, mutagenic, reprotoxic and cardiotoxicity properties, the use of DEHP in medical devices has been challenged by the European authorities [10-14]. This action has forced manufacturers to replace DEHP with alternative plasticizers (APs), such as tris(2-ethylhexyl) trimellitate (TOTM), di-(2-ethylhexyl) terephthalate (DEHT), di(isononyl)-cyclohexane-1,2-dicarboxilic acid (DINCH), di-(2-ethylhexyl) adipate (DEHA), acetyl tri-n-butyl citrate (ATBC), diisodecyl phthalate (DiDP), di-isononyl phthalate (DiNP), and di(2-propylheptyl) phthalate (DPHP).

In medical devices, the occurrence of alternative plasticizers is widely variable among various types of devices [1]. Some plasticizers have specific uses, for example DINCH or ATBC are mainly used in red blood cell PVC bags due to their capacity to prevent excessive

haemolysis during storage [15]. However, plasticizer use is constantly evolving as there is no reference to guide manufacturers in the choice and amount to be integrated into their products. Currently, toxicity data on these alternative plasticizers and information regarding leaching from medical devices for these alternative plasticizers are scarce or at most incomplete [16, 17].

Due to increasing concern regarding the leaching or migration of plasticizers from the medical devices into the patients, we aimed to identify the plasticizers present in indwelling medical devices and essential accessories commonly used in the pediatric ICU (PICU).

2. Materials and Methods

2.1 Chemicals and standard solutions

All organic solvents (purity more than 99%) such as Ethyl acetate (for LC LiChrosolv®) and n-hexane (GC SupraSolv®) were purchased from Merck KGaA (Darmstadt, Germany). The following standards (purity) were used for identification of predominant peaks: ATBC (98%), DEHA (99%), DiNP (99%), DiDP (99%), DPHP (98%), DEHT (95%), and TOTM (99.5%) were purchased from Accustandard (New Heaven, CT, USA). DINCH (99%) was received from BASF (Ludwigshafen, Germany). DEHP (≥99%), butylated hydroxytoluene (BHT; ≥99%), 2,2,4-trimethyl-1,3-pentanediol di-iso-butyrate (TXIB; 98.5%), 2,4-di-tert-butylphenol (DTBP; 99%), tris(2,4-di-tert-butylphenyl) phosphite (Irgafos 168, 98%), diisobutyl phthalate (99%), dibutyl phthalate (99%), octadecanoic acid, ethyl ester (≥ 99%), benzophenone, 4-phenyl- (99%) and deuterated internal standard (IS) 1,4-Di-benzyl Phthalate-d4 (DBzP-d4; 98%) were purchased from Sigma-Aldrich (Bornem, Belgium).

2.2. Sample collection and preparation

We collected a wide variety of PVC medical devices (*n*=97) daily used in the PICU of two academic hospitals. Thirty one samples (*n*=31) were from Hospital 1 (**Leuven, BE)** and sixty six samples (*n*=66) were from Hospital 2 (**Rotterdam, NL)**. Among these are endotracheal and nasogastric tubes, intravenous and -arterial catheters, bags containing fluids, blood (-products) or PN for intravenous administration, as well as tubbing used for hemodialysis, cardiopulmonary bypass and extracorporeal membrane oxygenation. The identified compounds are presented in Table 1. Some of these devices already specified on the label whether DEHP was present or not (Table 2 and 3).

Analyses of phthalate and alternative plasticizers in indwelling medical devices were performed according to the method described elsewhere [18], with slight modifications. From

our previous results, the mixture hexane: ethyl acetate (1:1) was the best extraction solvent for a mixture of several chemicals previously identified with a wide variety in polarity and chemical functionality (details are provided in Onghena et al. [18]). We cut small pieces (around 100 mg) from each plastic device. If the device had multiple plastic parts, we cut small pieces from each part and pooled them together as one sample. The samples were transferred to a clean empty glass tube. After adding 5 mL of solvent (hexane: ethyl acetate; 1:1), the samples were covered carefully (to avoid evaporation) and kept for 1 h at room temperature. Then, the samples were vortexed for 1 min. If the extracts were turbid, they were centrifuged (2500 g for 5 min) and the supernatant layer was collected. From the extract, we transferred 80 µL to a gas chromatography mass spectrometry (GC-MS) vial and added 20 µL internal standard (DBzP-d4) to correct for potential variations in the instrumental response and retention time. A volume of 2 µL of the extract was injected into the GC-MS.

2.3. Instrumental Analysis

The extracts were analyzed with an Agilent 6890 gas chromatograph coupled to an Agilent 5973 mass spectrometer operated in electron ionization (GC-EI-MS) and operated in scan mode. The quadrupole and ion source temperatures were set at 150 and 230°C, respectively. The electron multiplier voltage was 2200 V. The GC column was a 30 m × 0.25 mm × 0.25 µm DB-5 ms column (Agilent JW Scientific). The temperature of the oven was set at 60°C for 3 min, and was then increased to 300°C at a rate of 10°C/min where it was held for 15 min. The total run time was 42 min. Helium was used as a carrier gas at a constant flow rate of 1.0 mL/min. Since we performed an untargeted search, the MS was operated in full-scan mode from m/z 40 to 700. Standard solutions used to identify some of the plasticizers were injected separately to know the retention times and specific ions. For the other plasticizers, identification was done using the Agilent MSD Chemstation® for peak identification and the WILEY2009 mass spectra library.

2.4. Quality assurance/quality control

Preparation and storage of standard solutions were performed only with glass materials to prevent the extraction of phthalates and other plasticizers from plastics. The glassware was cleaned before use by rinsing three times with organic solvents (hexane: ethyl acetate, 1:1) and kept in the oven at 400°C overnight. Sample processing tubes or solvents were tested separately for background levels of contamination. None of the target chemicals was present

in the containers. After every sample, a solvent blank (hexane: ethyl acetate, 1:1) was injected to check for carryover.

3. Results

The specific ions and retention times for the identified compounds are presented in Table 1. Since the purpose was to present an overview of the current status regarding the use of plasticizers in medical devices used in the PICU, the study contains only qualitative results. The identified compounds in medical devices of two large academic hospitals are presented in Tables 2 and 3. The presence of DEHP was specified by the manufacturer on the package of some devices. These devices contained predominantly DEHP as a major peak. However, DEHP was measured as second or third dominant peak in several devices in which the presence of DEHP was not specified. Most probably, DEHP presence in the latter devices is a consequence of the DEHP use together with other plasticizers or as an impurity of TOTM technical mixture used in several devices.

3.1. Hospital 1: Leuven

Identified compounds varied between the samples (Table 2). Many of the analyzed samples contained mixtures of compounds, whereas for some samples no chemicals could be seen or identified (specified as ND and unknown in Table 2). Table 2 contains the details of all identified compounds, while Figure 1A is restricted to the three predominant compounds (based on high peak abundances) per sample. Some samples contained compounds that were not present in any of the other samples (marked as “others”, such as siloxanes, butylated hydroxytoluene, dihexyl azelate, irganox, etc., Table 2). Several other identified chemicals included citrates, sebacates, and adipates. Results obtained indicate a predominant use of DEHP (28%) as plasticizer, followed by “others” (28%), DEHA (15%) and TOTM (13%). Several plasticizers were used in less than 10% of the investigated samples (Figure 1A). Figure 2A shows the distribution of samples according to these compounds. DEHP was detected in 22 samples out of a total of 31 samples, followed by DEHT (10 of 31), DEHA (10 of 31), TOTM (9 of 31), ATBC (2 of 31), DiNP (2 of 31), DINCH (1 of 31), and DiDP (1 of 31).

3.2. Hospital 2: Rotterdam

As for the devices used in Leuven, identified compounds varied between the samples and many samples contained mixtures of compounds, whereas there were a few samples in which no chemicals could be seen or identified (Table 3). Table 3 contains the details of all identified compounds, while Figure 1B is restricted to three predominant compounds (based on high

peak abundances). Results obtained indicated a predominant use of DEHP (21%) as plasticizer, followed by "others" (44%; this group is higher compared to Leuven samples), DEHA (12%), TOTM (7%), and DEHT (7%). Several plasticizers were used in less than 5% of the investigated samples (Figure 1B). Figure 2B shows the samples distribution according to these compounds. DEHP was detected in 38 samples out of a total of 66 samples, followed by DEHA (22 of 66), DEHT (14 of 66), TOTM (11 of 66), ATBC (8 of 66), DPHP (4 of 66), DiNP (2 of 66) and DINCH (1 of 66).

4. Discussion

According to our results, and despite evolving regulatory regulations, DEHP is still the most common phthalate ester used in indwelling medical devices. DEHP was also found in the tubing made of PVC plasticized by TOTM. This can be explained by the supplier's difficulty in replacing it without loss of functionality, as well as by DEHP's well-known stabilization effect on the red blood cells conserved in plastic bags [19]. According to European directive [10], medical devices containing phthalates which are classified as carcinogenic, mutagenic or endocrine disruptors, of category 1 or 2, must be labelled. However, this regulation does not enforce a specific labelling for the presence of other plasticizers in the medical devices. Our results show that reference to labelling is insufficient to guarantee the absence of DEHP.

DEHA was the second most frequently detected compound in this study. Adipates, such as DEHA, are produced by diesterification of adipic acid with various alcohol groups [20]. Its classification as low temperature plasticizer makes DEHA a preferred plasticizer for cold solutions storage (for example, blood products). DEHA is relatively similar in structure and metabolism to DEHP, and is extensively used in household plastic food contact materials, and widely used in medical products and packaging [20, 21]. The available information on DEHA indicates that it is more lipophilic than DEHP, has a threefold greater potential to leach relatively to DEHP, and has the highest migration potential of all DEHP-free PVC plasticizers [17]. No information could be found relating to health risks of DEHA in medical devices, the plasticizer found to be the second most prevalent in the devices in this study.

The pattern of contamination observed for DEHP/ DEHA/ DEHT could be explained by the use of raw materials (plasticizers) of low purity. The amounts of impurities depend on the nature and the purity of the raw plasticizer used [22-23]. When considering samples with one main plasticizer, the popularity of DEHT becomes more pronounced, as it was detected in 24 samples out of a total of 97 samples. DEHT is the para isomer of DEHP. However, the structural

differences have important implications for the metabolism and consequential toxicological effects. DEHT undergoes a weak conversion to its primary metabolite, mono-ethylhexyl terephthalate (MEHT), and leading to a lower toxicity than DEHP [24]. No information could be found on the health risks due to the presence of DEHT in medical devices.

TOTM is an ester of trimellitic acid (1,2,4-benzene tricarboxylic acid) with a higher molecular weight than DEHP and a lower migration potential in aqueous solutions as compared with other plasticizers [17, 20]. The most common applications of TOTM are in medical products, specifically blood bags and infusion sets, but they are also used in packing, cables, floor, and wall coverings [20]. The presence of DEHP as an impurity in technical TOTM originates from the presence of ortho-phthalic acid as an impurity in the trimellitic acid that is used for the synthesis of TOTM. Similarly, the presence of para-phthalic (terephthalic) acid in the trimellitic acid used for the synthesis of TOTM may explain the high level of DEHT contamination found in medical devices when TOTM is used as a plasticizer. According to the results obtained, TOTM seems to be the plasticizer containing the highest abundances of DEHP and DEHT impurities. Our results agree with results obtained in PVC medical devices tested by Gimeno et al. [1] and Bourdeaux et al. [25]. Most of these alternative plasticizers are not well studied with regard to their potential effects on human health and the environment. Like phthalates, these alternative plasticizers are not chemically bound to the polymer and can leach out of the products.

ATBC is a non-volatile compound that has higher water solubility and is less lipophilic compared with other plasticizers, including phthalates [17, 20]. However, ATBC was found to migrate into enteral feeding solutions in significant quantities [17, 26]. ATBC is currently used in many products including cosmetics, flavoring agents 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 tubing [17, 20]. Effects from prolonged exposure to ATBC are largely unknown [20] and therefore further research is warranted.

DPHP is a relatively new phthalate plasticizer, which may be of concern when used as a plasticizer in medical devices, despite being less toxic than DEHP [17]. No information could be found on the risk on the health of DPHP in medical devices.

DINCH is the most recently developed alternative plasticizer for sensitive applications and is trademarked as Hexamoll DINCH by BASF, Ltd (Cheshire, UK) [27]. DINCH is obtained by the hydrogenation of the benzene ring in o-phthalates (such as DEHP) and it is used in the

manufacturing of enteral and hemodialysis tubing, bags, respiratory tubes, catheters, gloves and breathing masks [28]. Although the molecular weights of DINCH and DEHP are comparable, structural differences between the two lead to a lower PVC interaction with DINCH [29]. Because of relatively 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 [29]. Brought to the market as a 'sensitive alternative' to DEHP, DINCH has undergone extensive toxicological testing [17]. Research shows that migration of DINCH into enteral feeding solutions is eightfold lower than DEHP migration [26]. In the present study, DINCH was detected < 5% of the investigated samples (2 of 97) whereas DEHP was detected in 60 samples out of a total of 97 samples.

Analyses of DEHP alternatives are essential. A complete withdrawal of PVC in medical tubing and bags may be a good solution, especially when containing or transporting lipid solutions, and the use of PVC-free polymers may be the preferred alternative [30-32]. Hospitals are increasingly demanding PVC-free products thereby driving the research and development in the alternative polymer market. European manufacturers and suppliers are subjected to 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 [33].

Another important consideration is that a comprehensive switch to DEHP-free products in an ICU 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 are increasingly used in medical devices, it is important to weigh their potential health effects against those of DEHP, particularly in PICU and NICU settings. Appropriate labeling specifying the presence of alternative plasticizers is also required. Given the increased susceptibility of infants and children, as well as the known adverse health effects of DEHP, any DEHP-free alternative should be thoroughly evaluated based on comprehensive toxicological studies, monitoring for long-term health effects and standards of safety, as well as its functional effectiveness, cost-efficiency and regulatory compliance [34].

Recent investigations showed the occurrence of plasticizers in medical devices [1, 24, 25, 35, 36]. Human exposure to plasticizers is a matter of concern because certain plasticizers are known to be neurotoxic, carcinogenic and endocrine disruptors [37, 38]. Animal and human

data clearly suggest that children are more vulnerable to toxins than adults in general, and to DEHP and its metabolites in particular [2,3, 5,6]. Alternative plasticizers were considered to be safer than DEHP, but the data on safety are conflicting. Recent data suggest that some alternative plasticizers may have endocrine disrupting capacities, as well as neurotoxic and other toxic effects [39]. Alternative plasticizers are thus increasingly being used, though without assessment of potential toxicity at high exposure. The presence of either DEHP, and alternative plasticizers or both in many medical devices frequently used in the PICU is therefore highly relevant.

5. Conclusions

Our results suggest that children admitted to the ICU are exposed to a wide range of plasticizers, with a predominant presence of DEHP in medical devices, followed by DEHA, DEHT and TOTM. In view of the reported signs of toxicity with high DEHP exposure, this is a major concern. Also regarding the use of several alternative plasticizers there is the reason for concern, and potential toxicity should be thoroughly studied.

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Competing financial interest declaration

The authors report no conflicts of interest.

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Tables and Figures (captions):

Table 1: Specific ions and retention times for the identified compounds

Table 2: The identified Plasticizers in medical devices (academic hospital 1- Leuven)

Table 3: The identified Plasticizers in medical devices (academic hospital 2- Rotterdam)

Figure 1. Distribution of PVC medical devices sample parts (%) according to the plasticizer identified (most abundant three peaks in Hospital 1A and 2B).

Figure 2. Distribution of PVC medical devices sample according to major analytes analyzed in this study (Hospital 1A and 2B).

Table 1: Specific ions and retention times for the identified compounds.

Compounds	Acronyms	Molecular Formula	Molecular weight (g/mol)	CAS-Number	Retention time (min)	Ion 1 (m/z)	Ion 2 (m/z)	Ion 3 (m/z)
Butylated hydroxytoluene	BHT	$C_{15}H_{24}O$	220.35	128-37-0	13.4	205	220	145
2,2,4- trimethyl-1,3-pentanediol di-iso-butyrate	TXIB	$C_{16}H_{30}O_4$	286.41	6846-50-0	14.27	71	43	111
2,4-diphenyl-4-methyl-1-pentene	α -MSD	$C_{18}H_{20}$	236.35	6362-80-7	16.79	143	221	236
Ethanone-2,2-dimethoxy-1,2-diphenyl	DMPA	$C_{16}H_{16}O_3$	256.30	24650-42-8	17.35	151	105	225
Tributyl-O-acetyl citrate	ATBC	$C_{20}H_{34}O_8$	402.50	77-90-7	19.92	185	259	129
Di-(2-ethylhexyl) adipate	DEHA	$C_{22}H_{42}O_4$	370.57	103-23-1	20.98	129	112	147
Di-n-hexyl azelate	DnHA	$C_{21}H_{40}O_4$	356.54	109-31-9	21.49	171	255	213
Di-n-hexyl sebacate	DnHS	$C_{22}H_{42}O_4$	370.57	2449-10-07	22.11	185	269	227
Di-2-ethylhexyl-phthalate	DEHP	$C_{24}H_{38}O_4$	390.56	117-81-7	22.18	149	167	279
Di-isononylcyclohexane-1,2-dicarboxylate	DINCH	$C_{26}H_{48}O_4$	424.70	166412-78-8	22.40 to 24.40	155	127	281
Di-isononyl phthalate	DiNP	$C_{26}H_{42}O_4$	418.62	68515-48-0	23.25	293	149	167
Di-(2-ethylhexyl) terephthalate	DEHT	$C_{24}H_{38}O_4$	390.54	6422-86-2	23.56	261	149	167
Di-isodecyl phthalate	DiDP	$C_{28}H_{46}O_4$	446.67	26761-40-0	23.74 to 25.78	307	149	167
Di(2-propylheptyl) phthalate	DPHP	$C_{28}H_{46}O_4$	446.67	53306-54-0	23.87	149	167	307
1,4-Di-benzyl phthalate-d_4*	DBzP-d4	$C_{18}H_{22}N_2$	266.38	2298-55-7	24.21	91	107	153
Tris (2-ethylhexyl) trimellitate	TOTM	$C_{33}H_{54}O_6$	546.80	3319-31-1	30.18	305	323	193

* Deuterated Internal standard

Table 2: The identified Plasticizers in medical devices (Academic hospital 1- Leuven)

Code	Description	Company	Note	Predominantly Identified compounds based on peak abundance			
				Compound-1	Compound-2	Compound-3	Compound-4
L-01	Infusion set	Biomedica	Phthalate-free	TOTM	DEHT	DEHA	DEHP
L-03	Burette children	Biomedica		TOTM	DEHT	DEHP	
L-04	Burette transfusion	Hospira		TOTM	DEHT	DPHP	DEHA
L-05 *	Monitoring set	Edwards	Contains phthalates	DEHP			
L-06 *	Vamp junior	Edwards	Contains phthalates	DEHP	DEHT		
L-07	Baby flush	ICU Medical		TOTM	DEHA	DEHT	DEHP
L-08 *	Tracheal Tube 4.0 mm	Smiths/Portex	Contains phthalates	DEHP			
L-09 *	Tracheal Tube 6.0 mm	Smiths/Portex	Contains phthalates	DEHP			
L-10 *	Tracheal Tube 5,0 mm	Mallinckrodt/Covidien	Contains phthalates	DEHP	DEHT	DEHA	DiNP
L-11 *	Tracheal Tube 7,5 mm	Mallinckrodt/Covidien	Contains phthalates	DEHP	DEHA	ATBC	DEHT
L-12 *	Tracheal Tube 4.0 mm	Hudson/Teleflex	Contains phthalates	DEHP	DEHT		
L-13	Central venous catheter 4Fr - 8cm	Cook		Other (Irganox 1076)			
L-14	Pediatric jugular catheter set	Arrow		ND			
L-15	Folysil 6Fr	Coloplast		Other (Unknown)	DEHP	Other (Siloxanes)	
L-16	Bladder catheter CH16	Rush/Teleflex		Other (Siloxanes)	Other (BHT)		
L-17	Intravenous catheter 24G x 19mm	BD		Other (DnHA)	Other (DnHS)	Other (dodecanedioic acid dihexyl ester)	Other (Unknown)
L-18	Intravenous catheter 22G x 25mm	BD		Other (DnHA)	Other (DnHS)	Other (dodecanedioic acid dihexyl ester)	Other (Unknown)
L-21	Gastric tube 152cm 06Fr	Vygon		TOTM	DEHA	DEHP	DEHT
L-22 *	Gastric tube	Covidien - Argyle	Contains phthalates	DEHP	Other (Unknown)		
L-23	Trocart catheter	Covidien - Argyle		ATBC	Tributylphosphate	DEHA	DEHT
L-24	Round silicone fluted drain	Biovac		TOTM	Other (Siloxanes)	DEHT	DEHP
L-25	Pneumopericardial drainage set	Cook		Other (Irganox 1076)			
L-26	Intravenous catheter 22Ga x 25 mm	BD		Other (DnHA)	Other (DnHS)	Other (dodecanedioic acid dihexyl ester)	Other (Unknown)
L-31	Parenteral nutrition bag 1000ml	Baxter		DEHP	Other (BHT)		
L-33	Pediatric arterial canula ECMO	Sorin Group		DINCH	DEHP		
L-34 *	Single stage venous drainage cannula	Edwards	Contains phthalates	DEHP	DEHA	DiNP	BHT
L-35	CB BP50 Extracorporeal support pack Children 1/13	Medtronic		DEHP	DEHA	DiDP	Methyl oleate
L-36 *	Hollow Fiber Oxygenator	Medos	Contains phthalates	TOTM	DEHA	DEHP	DEHT
L-37	Prismaflex HF 20 Set	Hospal		DEHA	DEHP	TOTM	

L-38	Prismaflex ST 60 Set	Hospal	DEHP	DEHA	
L-39	Infant respiratory care system	Fischer & Paykel	TOTM	DEHT	DEHP

***** Some of these devices were already specified (label on the package) about the presence of DEHP

ND= no peaks detected

Table 3: The identified Plasticizers in medical devices (Academic hospital 2- Rotterdam)

Code	Description	Company	Note	Predominantly Identified compounds based on peak abundance			
				Compound-1	**Compound-2**	**Compound-3**	**Compound-4**
R-01	Venflon	Braun		Other (Methyl stearate)	Other (Irganox 1076)	Other (hexadecanoic acid)	
R-02	Intrarterial line lengthening piece	BD		DiNP			
R-03	Arterial line guidewire	Arrow		DEHP	Other (α -MSD)	Other (BHT)	
R-04*	Ventilator hose High frequency oscillator	Viasys	Contains Phthalates	DEHP	Other (2-(2H-benzotriazol-2-yl)-4,6-bis (1,1-dimethylpropyl)phenol	Other (diphenylmethane diisocyanate)	
R-05	Ventilator hose	Fisher&Paykel		DEHP	Other (methyl stearate)	Other (ethylhexyl benzoate)	
R-07	Bladder catheter	Bard		Other (Siloxanes)			
R-08	bone needle	Vidacare		TOTM	DEHP	DEHT	DEHA
R-09	Central venous Line Multistar	Vygon		Other (Irganox 1076)	Other (Miconazole)		
R-10	Tracheal canula portex blueline	Smiths medical		DEHP	Other (7,9-di-tert-butyl-oxaspiro(4,5)deca-diene-2,8-dione)		
R-11	Tracheal canula portex bivona	Smiths medical		Other (Siloxanes)			
R-12	Central venous Line Multicath	Vygon		Other (alkene like)	Other (2-(2H-benzotriazol-2-yl)-4,6-bis (1,1-dimethylpr	Other (diphenylmethane diisocyanate)	Diethyl phthalate

					opyl)phenol		
R-13	Dasconlijn	Vygon		DEHA			
R-14*	pressure device central line CVD	Argon	Contains Phthalates	DEHP	DPHP	Other (BHT)	TXIB
R-15*	pressure device venous line	Argon	Contains Phthalates	DEHP	Other (BHT)	Other (TXIB)	
R-16	pressure device arterial line	Argon		DEHP	Other (TXIB)	Other (BHT)	siloxanes
R-17*	Suctioning probe	Covidien	Contains Phthalates	DEHP	Other (phthalic acid, isobutyl isopropyl ester)	DEHA	
R-18*	Closed suctioning system	Kimberley-Clark	Contains Phthalates	DEHP	DEHA	TOTM	Benzophenone
R-19	Gloves non-sterile	Ansell		Other (BHT)			
R-20	gloves non-sterile, latex free	?		Other (BHT)			
R-21	gloves sterile	Ansell		Other (Dodecanoic acid)	Other (linoleic acid)		
R-22	gloves sterile, latex-free	Mölnlycke		Other (hexadecanamide, n-phenyl)	Other (dehydroabietic acid)	Other (carbodiimide, diphenyl)	dehydroabietal
R-23	intravenous lengthening line (light-protected)	Codan		ND			
R-25	Infusion bag medication	Baxter		DEHP	Other (BHT)		
R-27*	Blood transfusion bag	Fresenius Kabi	Contains Phthalates	DEHP	Other (Ethylhexyl benzoate)		
R-28	intravenous lengthening line	Codan		TOTM	DEHT	DEHP	DEHA
R-29	intravenous catheter	Unomedical		ND			
R-30	Enteral feeding drain	Covidien		Other (Siloxanes)			
R-31*	Larynx mask	LMA	Contains Phthalates	DEHP	TOTM	DEHT	DEHA

R-32	gastric probe PVC	Nutricia		Other (BHT)	DEHP	DEHA	Methyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate
R-33	gastric probe Silicon	Vygon		Other (Siloxanes)			
R-34	gastric probe RX PVC	Vygon		TOTM	DEHT	DEHP	BHT
R-35	Mic-key lengthening probe	Mediline		Other (BHT)	Other (Irganox 1076)		
R-36	Intravenous line (PCA pump)	Codan		TOTM	DEHA	DEHP	DEHT
R-37	Nasal prongs	Fisher&Paykel		Other (Siloxanes)			
R-38	Umbilical catheter	Vygon		Other (Irganox 1076)			
R-40*	Nasal prongs	Teleflex	Contains Phthalates	DEHP	Other (BHT)	ATBC	DEHA
R-41	intravenous lengthening line	BD		TOTM	DEHT	DEHP	DEHA
R-42	Nasal prongs optiflow	Fisher&Paykel		Other (bumetrizole)			
R-43	Port-a-cath needle	Braun		Other (Irganox 1076)			
R-44	pleural drain	Cook		Other (Irganox 1076)			
R-46	rectal canula	Rusch		DEHT	DEHA		
R-47	Replogle tube	Covedien		ATBC	Other (tributyl aconitate)	DEHA	DEHP
R-48	duodenal probe	vygon		Other (Siloxanes)			
R-49	enteral feeding lengthening probe	Macosta Meditea		DEHA	TOTM	DEHP	DEHT

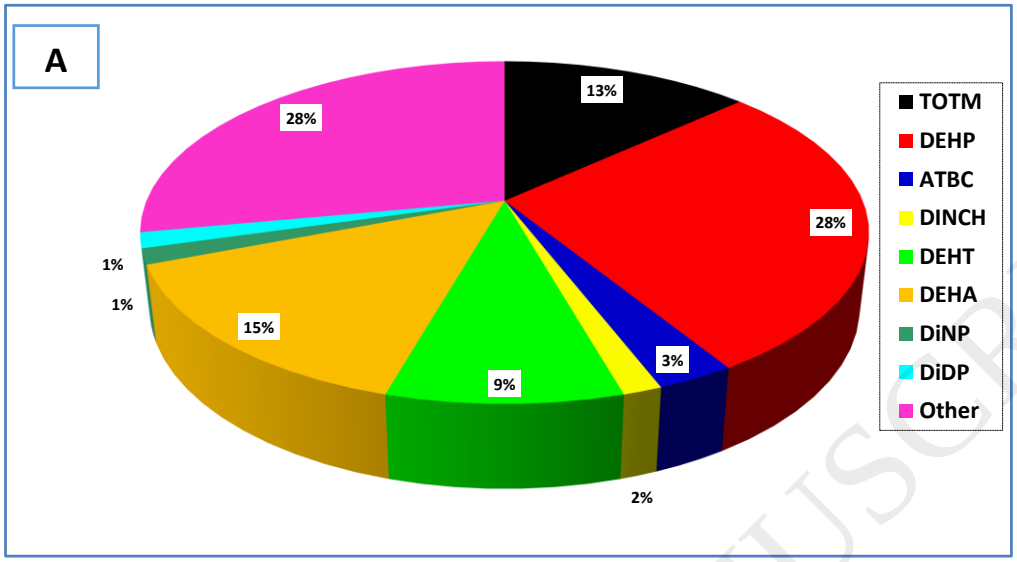
R-50	Swan-ganz catheter	Edwards		DEHA	TOTM	ATBC	DEHT
R-51	pleural drain trocar	Covidien		ATBC	DEHA	Other (Tributyl phosphate)	DEHT
R-53*	tracheal tube no cuff silicon	Smiths medical	Contains Phthalates	DEHP			
R-54*	tracheal tube with cuff	Smiths medical	Contains Phthalates	DEHP			
R-55*	tracheal tube no cuff Ivory	Smiths medical	Contains Phthalates	DEHP			
R-57*	Suctioning probe	Covidien	Contains Phthalates	DEHP	Other (ethylhexyl benzoate)	DEHA	
R-58	Bladder catheter	Covidien		Other (Siloxanes)			
R-60	intravenous 3 way connection line	BD		DINCH			
R-61*	wound drain	Medinorm	Contains Phthalates	DEHP	DiNP	DEHA	
R-62*	suctioning probe	Covidien	Contains Phthalates	DEHT	DEHP		
R-63	ECMO canula venous	Medtronic		Other (diphenyl methane diisocyanate)	Other (BHT)		
R-65	Dialysis catheter	MEdcomp		Other (Irganox 1076)	Other (BHT)	Other (butylstearate)	Diphenylmethane diisocyanate
R-67	ECMO canula	Avalon		ATBC	DEHA	Other (diphenylmethane diisocyanate)	Siloxanes
R-71	Tracheal canula Shiley	Tyco Healthcare Group		DEHP	Other (benzophenone)	DPHP	TOTM
R-72	Tracheal canula Tracoe	Tracoe		ATBC	DEHA	Other (bis-(2-ethylhexyl) azelate)	Tributyl aconitate

R-74	Enteral probe lengthening	Nutricia		TOTM	DEHT	DEHP	
R-75	Intravenous catheter	HOspira		ND			
R-76	Intravenous catheter	BD		Other (Irgafos 168)	Other (Advastab 800)	Other (Oxidized Irgafos 168)	
R-77	Gastrostomy probe	Nutriticia		Unknown	Other (siloxanes)		
R-78 *	Tracheal tube	Rusch	Contains Phthalates	DEHP	DEHA	DEHT	TXIB
R-79	Tracheal tube	Parker		DEHP	DiNP	Other (ethylhexyl benzoate)	ATBC
R-80 *	Tracheal tube	Covidien	Contains Phthalates	DEHP	DEHA	DEHT	BHT

* Some of these devices were already specified (label on the package) about the presence of DEHP

ND= no peaks detected

Figure 1. Distribution of PVC medical devices sample parts (%) according to the plasticizer identified. Most abundant three peaks in (A) Hospital 1 and (B) Hospital 2. Some samples are not included since no peaks were detected. Other= E.g. BHT, Siloxanes, Irganox, .. See Tables 2 and 3 for detailed information.



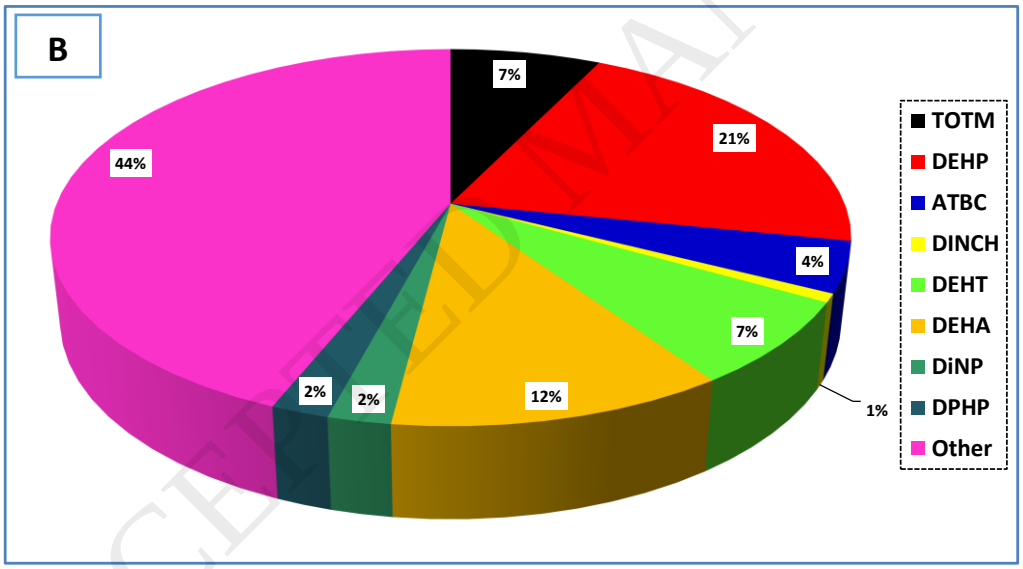


Figure 2. Distribution of PVC medical devices sample according to major plasticizers identified in this study. (A) Hospital 1 and (B) Hospital 2.