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Experimental study on infusion devices containing polyvinyl chloride: To what extent are they di(2-ethylhexyl)phthalate-free?

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ABSTRACT

The use of medical devices containing highly criticized phthalates including di(2-ethylhexyl) phthalate (DEHP) has been challenged by European directive 2007/47/CE, put into effect in March 2010. New plasticizers are now being used to soften PVC in medical devices: trioctyltrimellitate (TOTM), di-isononyl-cyclohexan-1,2-dicarboxilate (DINCH) and di(2-ethylhexyl) terephthalate (DEHT). To quantify DEHP in nine DEHP-free medical devices made of PVC softened by alternative plasticizers, high performance liquid chromatography analysis with ultraviolet detection at 220 nm wavelength was achieved. An NMR spectroscopy was performed to confirm DEHP presence. Only two medical devices out of the nine tested were truly without DEHP. One of them showed traces of DEHP exceeding the threshold contamination of 0.1% in plastic mass set by REACH regulations. TOTM plasticizer is still incriminated when polyvinyl-chloride (PVC) is contaminated with DEHP. Manufacturers must verify the purity of their raw material, not only on PVC, but also on other soft plastics entering into the composition of medical infusion devices. The clinical consequences of exposure to certain levels of DEHP have not been evaluated. A solution could be to use alternative PVC-free materials.

1. Introduction

Phthalates are compounds obtained by phthalic acid esterification. They are used as polyvinyl chloride (PVC) plasticizers. They are added to the PVC polymer, up to a maximum concentration of about 40%. Plasticizers are found in many PVC articles: vinyl flooring, paint, food wrappers, cosmetics, and medical devices (MD). Until recently, the most commonly used plasticizers were phthalates, especially di(2-ethylhexyl) phthalate called DEHP (CAS No 117-81-7) (Fig. 1). Use of DEHP-containing medical devices results in exposure to DEHP as reflected by elevated urinary levels of MEHP (Green et al., 2005).

Attention has been focused on the carcinogenic risks of products containing DEHP as a plasticizer. More recently, it has been pointed out that DEHP seems to be an endocrine disruptor (Akingbemi et al., 2004; Meeker et al., 2007; Crain et al., 2008). Effects on reproductive function and growth were observed in *in vitro*, animal and human studies (Lovekamp-Swan and Davis, 2003; Latini et al., 2003). The 2008 report by the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) highlighted DEHP toxicity from several animal and some human studies and also suggested using less toxic alternatives.

Following these considerations, the use of medical devices containing targeted phthalates including DEHP has recently been challenged by European directive 2007/47/EC, effective since March 2010.

Several alternatives are currently available (Fig. 1), such as trioctyltrimellitate (TOTM, CAS No 3319-31-1), di-isononyl-cyclohexan-1,2-dicarboxilate (DINCH, CAS No 166412-78-8) or di(2-ethylhexyl) terephthalate (DEHT, CAS No 6422-86-2), with an improved toxic profile for TOTM and DEHT (Barber and Topping, 1995; Gray et al., 2000; Kambia et al., 2004; Shea, 2003). These alternative plasticizers are more strongly bound to PVC than DEHP so their leaching is reduced (Ito et al., 2008; Kambia

Abbreviations: DEHP, di(2-ethylhexyl) phthalate; DEHT, di(2-ethylhexyl) terephthalate; DINCH, di-isononyl-cyclohexan-1,2-dicarboxilate; DNHP, di-n-heptyl phthalate; PE, polyethylene; PET, polyethylene terephthalate; PU, polyurethane; PVC, polyvinyl chloride; TOTM, trioctyltrimellitate.

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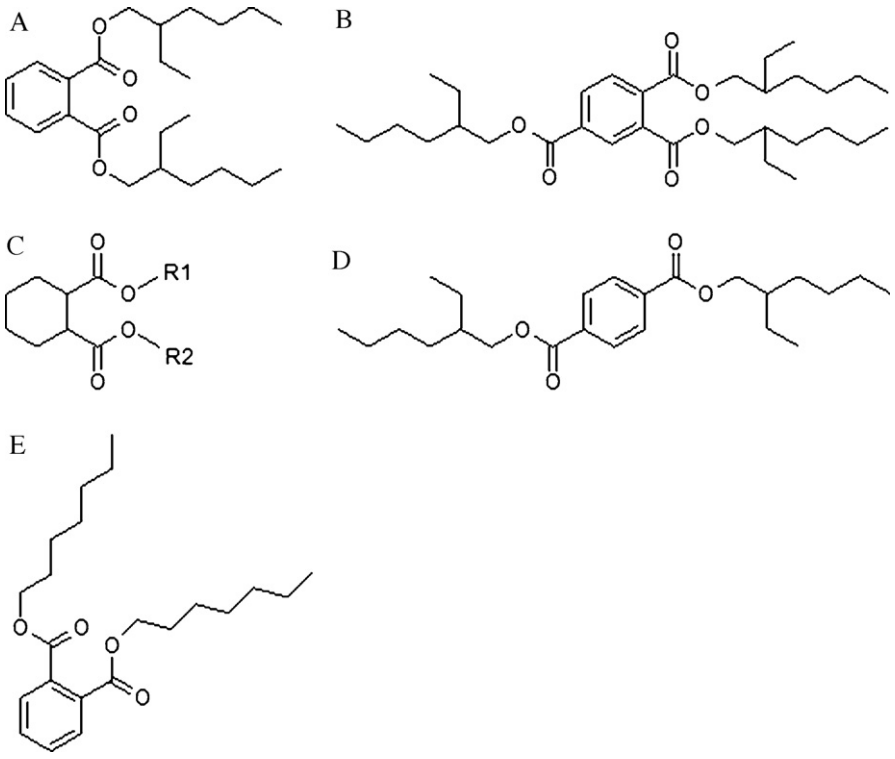

Fig. 1. Semi-developed formula of DEHP (1A), TOTM (1B), DINCH (1C), DEHT (1D) and DNHP (1E).

et al., 2001; Loff et al., 2000; Takehisa et al., 2005; Welle et al., 2005).

The use of medical devices containing alternative plasticizers should be generalized although the question should be raised concerning their composition and the continued use of DEHP in smaller quantities but over the contamination threshold of 0.1% in the mass as defined by the European regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemical substances (REACH) (Regulation 1907/2006, 2006). We therefore decided to launch a study to find DEHP in DEHP-free devices.

2. Materials and methods

2.1. Medical devices

Six infusion sets and three extension sets from seven manufacturers were analyzed. According to these manufacturers, they were DEHP-free. The prototypes have individual, sterile packaging. We analyzed all flexible plastics made of PVC. Three different alternative plasticizers are used in these products: TOTM, DINCH and DEHT. The medical devices involved are indicated in Table 1.

2.2. HPLC method

DEHP and di-n-heptyl phthalate (DNHP, CAS No 3648-21-3) (Sigma Aldrich, Saint Quentin Fallavier, France) were used as analytical standards and as internal standard (IS) respectively (Kambia et al., 2001). DEHP concentration was determined at room temperature using a high-performance liquid chromatographic (HPLC) system equipped with a constant flow-rate pump LC 10-AS (Shimadzu, Kyoto, Japan), a manual injection valve, and a constant-wavelength ultraviolet light detector SPD 10-AVP (Shimadzu, Kyoto, Japan), all of which were connected to a data integrator C-R8A (Shimadzu, Kyoto, Japan). We used a column Alltima® $HPC_{18}HL3\mu m$ (Grace Davison Discovery Science, Lokeren – Belgium) with a constant section of 3 mm for a length of 15 cm. The mobile phase was a mixture of acetonitrile HiPerSolv CHROMANORM HPLC gradient grade (VWR, Leuven, Belgium) and ultrapure water (Purelab UHQ ELGA, France) acidified with 0.05% orthophosphoric acid 85% (Prolabo, Paris, France) (92:8, vol/vol). The flow rate was 1.1 mL/min and the injection volume was 20 μL. The detection wavelength was set at 220 nm.

Standard solutions of analytical grade DEHP 1 mg/mL and DNHP 1 mg/mL were prepared in acetonitrile. Working standards were extemporaneously prepared at concentrations of 0.1, 0.2, 0.5, 1, 2,

Table 1
Medical devices containing alternative plasticizers.

Manufacturer	Medical device	Brand name	Reference	Tubing plasticizer
AseptInMed	Infusion set	Medi-Globe *Uni*'Perf	200928	DINCH
AseptInMed	Extension set	Uni Fold	201035	TOTM
Baxter	Infusion set	Administration Set	UMC3318	TOTM
B.Braun	Infusion set	Intrafix Safeset G	4063009	DEHT
Cair LGL	Extension set	Unicath	PNX3120	DINCH
Cair LGL	Extension set	Biocath	PBX3115	TOTM
Codan	Infusion set	L86P	43.4535	TOTM
Doran	Infusion set	Kis1	Kis1	TOTM
Sendal	Infusion set	Perfusend I	A94	TOTM

Table 2
Results of the selectivity study.

Product	Retention time (min)
IS	5.7
DEHP	8.3
DEHT	16.4
TOTM	60.3

Table 3
Validation of the assay method.

Parameters	Values
Linearity range (μg/mL)	0.20–10.00
y-Intercept	0.473 ± 0.070
Slope	0.781 ± 0.015
Correlation coefficient (*r*)	0.997
Determination coefficient (r^2)	0.994
LOD (μg/mL)	0.22
LOQ (μg/mL)	0.44

LOD, limit of detection; LOQ, limit of quantification.

5 and 10 μg/mL using the above stock solutions diluted to a concentration of 200 μg/mL in acetonitrile. These solutions were used to establish a calibration plot. The DEHP concentration in the samples was obtained by extrapolation from this calibration plot. None of the materials or solvents used to prepare samples and conduct chromatographic analysis contained DEHP. To minimize the risk of contamination with DEHP during sample handling and analysis, all the glassware used in the study was washed with tetrahydrofuran (VWR, Leuven, Belgium), then methanol HPLC grade (Fischer Scientific, Loughborough, England) and finally rinsed with ultrapure water. All the other reagents were of analytical grade or better.

Our assay method was validated by determining the following parameters: specificity, linearity, limits of detection (LOD) and quantification (LOQ). The DEHP assay method was specific. DEHP retention time was 8.3 min (Fig. 2 and Table 2). The results of the validation method are shown in Table 3.

2.3. HPLC assays

A sample of about 50 mg was removed from each flexible piece of PVC plastic (infusion tubing and/or drip chamber). Each sample was precisely weighed (Mettler Toledo XP504) and dissolved in 100 μL of IS stock solution with 900 μL of THF. After 1 h, 200 μL of this vortexed solution was diluted with the same volume of methanol in order to precipitate PVC. 900 μL of acetonitrile was added to 100 μL of the supernatant and this solution was centrifuged at 16,000 × *g* for 5 min (Eppendorf Centrifuge 5415), then 20 μL of the supernatant was injected into the column. After 70 min, chromatograms were obtained. Concentrations were expressed in percentage of plastic mass. For a 50 mg sample, 1 μg/mL matches 0.04% of DEHP in plastic mass. Each reference was analyzed three times. With this method, LOD was determined at 0.22 μg/mL corresponding to 0.009% of DEHP in plastic mass for a sample of 50 mg, and LOQ at 0.44 μg/mL corresponding to 0.018% of DEHP in plastic mass for a sample of 50 mg.

2.4. ^{1}H NMR analysis

In order to confirm HPLC positive results (DEHP presence over 0.1% in plastic mass), a NMR spectroscopy Avance II, 500 MHz (BRUKER BioSpin, France) was performed. A pure DEHT solution was used as negative control and treated like the other samples, whereas the positive control was an infusion tubing made of PVC-DEHP. Ten grams of each sample flexible PVC plastic were cut off and gradually dissolved by THF. A methanol volume was added respecting the THF–methanol quantitative ratio of the extraction protocol ($volume_{MeOH} = 12\ volume_{THF}$). The final solution was centrifuged and the supernatant withdrawn and evaporated on a hotplate to obtain pure liquid DEHP. The sample obtained was diluted with deuterated methanol D_4 < 0.03% (Eurisotop, Saint-Aubin, France) in an NMR tube and analyzed by ^{1}H NMR spectrocopy.

3. Results

3.1. HPLC analysis

Results of HPLC analysis are shown in Table 4. For a 50 mg sample, DEHP presence was undetectable in only two medical devices (AseptInMed reference 200928 and Codan reference 43.4535). Two medical devices presented non-quantifiable DEHP traces (Cair LGL PNX3120 and B.BRAUN Intrafix safeset G reference 4063009). Five medical devices had quantifiable DEHP traces, one presenting rates over 0.1%. Sendal reference A94 infusion tubing contained

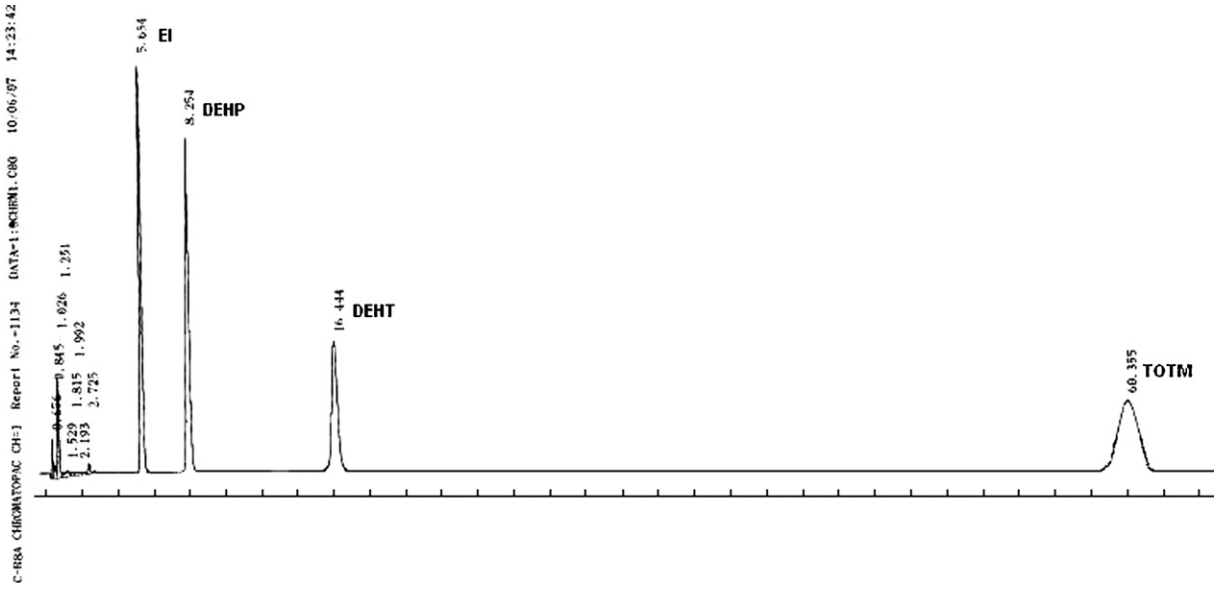

Fig. 2. Results of the selectivity analysis - chromatogram of pure product mixture (10 μg/mL of each).

Table 4
Results of DEHP extraction in drip chambers and infusion tubings.

Manufacturer	Reference	Batch	Tubing plasticizer	Analyzed site	Number of trials	Median (%)	MAD (%)	Min (%)	Max (%)
AseptInMed	200928	1010454C	DINCH	Drip chamber	3	ND[a]	ND[a]	ND[a]	ND[a]
				Infusion tubing	3	ND[a]	ND[a]	ND[a]	ND[a]
	201035	A091116	TOTM	Infusion tubing	3	0.0575	0.0043	0.0456	0.0586
Baxter	UMC3318	10D15V278	TOTM	Drip chamber	3	ND[a]	ND[a]	ND[a]	ND[a]
				Infusion tubing	3	0.04677	0.0056	0.0402	0.0565
B.Braun	4063009	9F10278A13	DEHT	Drip chamber	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
				Infusion tubing	3	ND[a]	ND[a]	ND[a]	ND[a]
	4063009	0A02278A14	DEHT	Drip chamber	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
				Infusion tubing	3	ND[a]	ND[a]	ND[a]	ND[a]
	4063009	0C20278A13	DEHT	Drip chamber	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
				Infusion tubing	3	ND[a]	ND[a]	ND[a]	ND[a]
Cair	PNX3120	09I14-T	DINCH	Infusion tubing	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
LGL	PBX3115	09I17-T	TOTM	Infusion tubing	3	0.0340	0.0015	0.0320	0.0363
Codan	43.4535	K809126-1	TOTM	Drip chamber	3	ND[a]	ND[a]	ND[a]	ND[a]
				Infusion tubing	3	ND[a]	ND[a]	ND[a]	ND[a]
Doran	KIS 1	prototype	TOTM	Drip chamber	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
				Infusion tubing	3	0.0214	0.0014	0.0191	0.0246
Sendal	A94	9D05353	TOTM	Drip chamber	3	NQ[b]	NQ[b]	NQ[b]	NQ[b]
				Infusion tubing	3	0.2484	0.0198	0.2263	0.2782

MAD, median absolute deviation.
[a] ND < 0.22 μg/mL i.e. 0.009% of DEHP in plastic mass for a sample weight of 50 mg.
[b] NQ < 0.44 μg/mL i.e. 0.018% of DEHP in plastic mass for a sample weight of 50 mg.

0.248 ± 0.020% of DEHP in plastic mass but no quantifiable presence in its drip chamber. Results from B.Braun devices were confirmed by analyses of other batches.

3.2. ^{1}H NMR analysis

Fig. 3 shows an ^{1}H NMR spectrum confirming the presence of DEHP traces in both infusion sets tested (B.Braun reference 4063009 drip chamber and Sendal reference A94 infusion tubing).

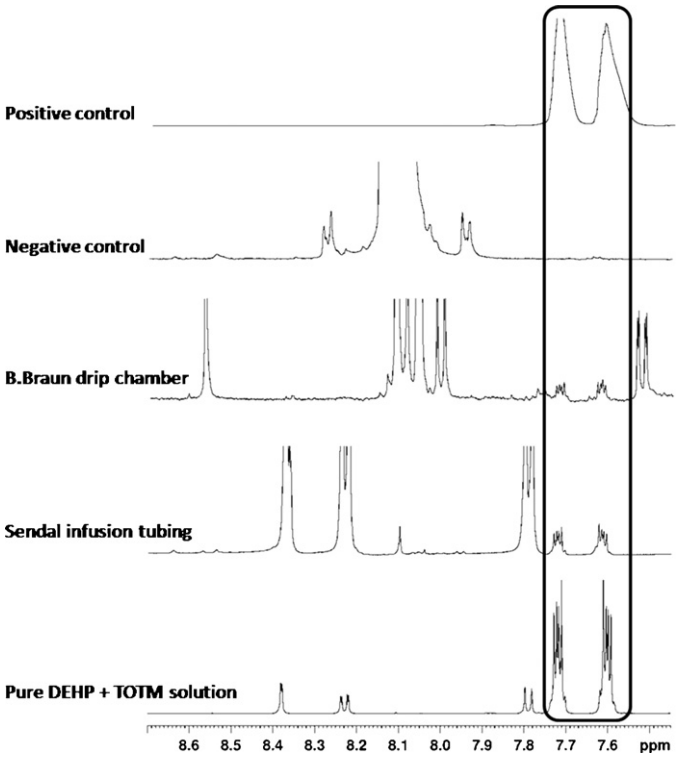

Fig. 3. ^{1}H NMR spectra (aromatic chemical shift). In the window, multiplets corresponding to DEHP aromatic protons.

4. Discussion

The HPLC/UV analytical method used in this study makes it possible to detect DEHP concentrations reaching and exceeding the contamination threshold defined by the REACH Regulation even if the liquid chromatography–tandem mass spectrometry method is the one currently used to quantify DEHP (Ito et al., 2005; Takatori et al., 2004). A few remarks can be made. Firstly, analysis time was very long (60.3 min) to identify DEHP while observing the TOTM peak. Only DINCH was not characterized by the analytical method as it does not absorb in ultraviolet because of its structure and needs gas chromatography/mass spectrometry for quantification (Ezerskis et al., 2007; Sannino, 2010). Secondly, as regards detection wavelength, Kambia et al. (2001) confirmed DEHP presence with HPLC/UV at 202 nm whereas Bagel-Boithias et al. (2005) detected it at 254 nm. In this study, the detection wavelength was 220 nm so as to detect very low quantities of DEHP with better specificity than at 202 nm and better sensitivity than at 254 nm. Thirdly, it is essential to distinguish DEHP from DEHT. The HPLC/UV analytical method means these two *para* isomers can be separated. To specifically characterize the DEHP peak obtained on our chromatographic profiles, an NMR spectroscopy was performed. This second analytical method separates DEHP, DEHT and TOTM and reveals that each molecule has a different symmetry with a characteristic ^{1}H spectrum. DEHP aromatic protons present two characteristic multiplets at chemical shifts of 7.60 and 7.71 ppm, which are not to be found in the DEHT or TOTM spectrum. Therefore, these multiplets encountered in the samples from the Sendal and B.Braun devices confirm our HPLC results concerning the presence of DEHP although not quantifiable for B.Braun.

According to the results of this study, only two medical devices out of the nine DEHP-free tested are devoid of DEHP. One medical device showed DEHP concentrations higher than 0.1% in plastic mass.

DEHP traces less than the quantification threshold were found in the drip chambers of B.Braun, Doran and Sendal infusion sets. This part of the device is not made of plasticized PVC but of polystyrene and styrene-butadiene copolymer. This result suggests that DEHP can be found in components other than the tubing - this is one of the major findings of this study. The manufacturer's certificate must cover the whole device and not only the tubing. To our knowledge,

no other study on the leaching of DEHP has focused on this point. The Sendal infusion set also showed DEHP traces of over 0.1% in plastic mass. In this set, DEHP was found in the tubing made of PVC plasticized by TOTM. It should be noted that TOTM plasticizer is still incriminated when PVC is contaminated with DEHP. Only one manufacturer uses TOTM devoid of DEHP. DEHP presence can be due to contamination of the production line or of the raw chemical products.

According to European directive 2007/47/EC, when medical devices contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, they must be so-labeled. But this regulation does not enforce any specific labeling in the case of contamination by any chemical product. We have highlighted contamination in one medical device. Our results show that reference to labeling is insufficient to guarantee the absence of DEHP.

Another approach to avoid exposure to DEHP is to use PVC-free devices. Several materials were assessed. For example, fewer interactions with contact media were observed with inert polymers like polyethylene terephthalate (PET) or polyamide (Stoffers et al., 2004). However, the results of this study showed the presence of DEHP in PVC-free components. Care should also be taken with DEHP-free materials. Some polymers are not suitable for medical application: for example with its rigid mechanical properties, PET can hardly be used for flexible tubes or bags. Polyethylene (PE) and polyurethane (PU) seem to be more appropriate. It is noteworthy that co-extruded or multilayer (with DEHP included) tubing do not exclude DEHP exposure. Loff et al. (2004) and Bagel-Boithias et al. (2005) showed that co-extruded PVC/PU or PVC/PE lines and triple-layer tubing contained similar amounts of DEHP to PVC tubing.

5. Conclusion

Finally, this study demonstrates that DEHP can be present at low concentrations in several devices presented as DEHP-free. The DEHP concentrations found are above 0.1% but nevertheless remain relatively low. This result raises two questions. Firstly, the leaching of DEHP from these devices during contact with lipophilic substances must be investigated to measure patient exposure. Secondly, the clinical impact of such exposure should be assessed.

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