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Effects of flow rate on the migration of different plasticizers from PVC infusion medical devices

Flow rate impact on plasticizers' migration

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Abstract

Infusion medical devices (MDs) used in hospitals are often made of plasticized polyvinylchloride (PVC). These plasticizers may leach out into infused solutions during clinical practice, especially during risk-situations, e.g multiple infusions in Intensive Care Units and thus may enter into contact with the patients. The migrability of the plasticizers is dependent of several clinical parameters such as temperature, contact time, nature of the simulant, etc... However, no data is available about the influence of the flow rate at which drug solutions are administrated. In this study, we evaluated the impact of different flow rates on the release of the different plasticizers during an infusion procedure in order to assess if they could expose the patients to more toxic amounts of plasticizers. Migration assays with different PVC infusion sets and extension lines were performed with different flow rates that are used in clinical practice during 1h, 2h, 4h, 8h and 24h, using a lipophilic drug simulant.

From a clinical point of view, the results showed that, regardless of the plasticizer, the faster the flow rate, the higher the infused volume and the higher the quantities of plasticizers released, both from infusion sets and extension lines, leading to higher patient exposure. However, physically, there was no significant difference of the migration kinetics linked to the flow rate for a same medical device, reflecting complex interactions between the PVC matrix and the simulant. The migration was especially dependent on the nature and the composition of the medical device.

Introduction

In the field of infusion, numerous medical devices, such as infusion sets and extension lines are used in various simple or complex assemblies. Most of them are manufactured in PVC plasticized with alternatives to di-(ethylhexyl)-phthalate (DEHP) plasticizers, e.g. di-(ethylhexyl)-terephthalate (DEHT), di-isononyl-1,2-cyclohexane-dicarboxylate (DINCH) or trioctyl trimellitate (TOTM) and diisononyl phthalate (DINP). They have greatly replaced DEHP since it is likely to present a danger to the patient, and has now been classed as a CMR1b risk substance due to its effects on reproduction and fertility (1). Thus, it now must not exceed 0.1% by mass of the plasticized material, as defined

59 by the European regulation concerning the Registration, Evaluation, Authorization and Restriction
60 of Chemical substances (REACH). Furthermore, according to decree of 13th April 2017, its use in
61 tubings used in pediatric, neonatal, and maternity units has been restricted in France above a
62 threshold level of 0.1% (2)

63
64 However, only very limited data is available regarding the risk associated to the migration of the
65 alternative plasticizers from the medical devices, especially in at risk-situations like multiple
66 infusions in Intensive Care Units (ICU). To assess the exposure risk of inpatients, the evaluation of
67 their migration in such conditions is required. An infusion model was developed to estimate if a
68 medical device could be considered safe for infusion use according to the leaching of plasticizers (3).
69 Nevertheless, this model doesn't take into account of the flow rate at which drug solutions are
70 administrated to the patients, thus considering the exposure risk to be the same whatever the flow
71 rate of the infusion. Bagel et al demonstrated that the extraction of DEHP was encouraged in static
72 conditions (4) but no study has evaluated the influence of this parameter with alternative
73 plasticizers.

74 The aim of this work was to evaluate the impact of different flow rates on the release of four
75 plasticizers (TOTM, DINP, DEHT and DINP) during an infusion and to assess different infusion rates
76 that could expose the patient to more toxic amounts of plasticizers. From this basis, it could be
77 discussed whether the infusion model should be adapted and eventually if reduction factors linked
78 to the flow rate should be applied, correcting the specific migration with low or high flow rates (as it
79 has been done in the regulation 10/2011 (5) with food containing more than 20% fat).

80 To this end, we tested different flow rates usually applied in clinical practice through
81 infusion sets and extension lines. This study should finally help us to understand which mechanisms
82 govern migration phenomena of alternative plasticizers.

83

84 **Materials and methods**

85

86 **Samples**

87 MDs used for the migration assays were extension lines and infusion sets, which are commonly
88 used in the field of infusion. They were selected specifically because they contain one specific
89 different plasticizer each (TOTM, DEHT, DINCH or DINP) without any trace of carcinogenic,
90 mutagenic, reprotoxic 1b (CMR1b) phthalates, as announced by their manufacturer. To allow

91 correct comparability, each device was also chosen so as to have the same technical features in
 92 terms of the tube thickness (which is approximately 0.75mm for the extension lines and 0.6mm for
 93 the infusion sets).

94 The characteristics of the chosen medical devices are presented in tables 1 and 2.

95

96 **Table 1:** characteristics of PVC tubings from extension lines used in the migration study

Supplier	Cair LGL	Codan	B Braun	Sendal	Cair LGL	Cair LGL
Reference	PES 3301 M	E-87 P	0086670 D	Prolonsend	PN 3301 M	PN 3101 M
Batch	15D13T	H71654-1	14N02F8SPA	03446	13E21-TN	12H07-TN
Designation	EL 1	EL 2	EL 3	EL 4	EL 5	EL 6
Length (cm)	13.9	96.5	11.2	11.0	10.2	10.5
Weight of PVC tubing (mg)	1286.8	2837.8	1050.4	893.1	992.0	506.8
Inner diameter (cm)	0.25	0.10	0.25	0.30	0.25	0.10
Internal surface (cm²)	10.91	30.30	8.79	10.36	8.01	3.30
Volume (mL)	0.682	0.757	0.550	0.777	0.500	0.082
Co-extruded (PVC/PE)	Yes	No	No	No	No	No
Announced plasticizer	TOTM	TOTM	DEHT	DINP	DINCH	DINCH

97

98 **Table 2:** characteristics of PVC tubings from infusion sets used in the migration study

Supplier	B Braun	CareFusion	Doran International	Codan
Reference	4063007	A64	INFU-R3	43.4535
Batch	039615B13A8421	0396	1411247	L85603-1
Designation	IS 1	IS 2	IS 3	IS 4
Length (cm)	179.0	145.7	181.7	173.8
Weight of PVC tubing (mg)	12975.5	11470.7	15052.2	12258.5
Inner diameter (cm)	0.27	0.27	0.25	0.30
Internal surface (cm²)	154.6	124.4	141.5	170.3
Volume (mL)	10.4	8.5	8.8	13.3
Co-extruded (PVC/PE)	No	No	No	No
Announced plasticizer	DEHT	DINP	DINCH	TOTM

99

100

101 **Migration assays**

102

103 **Analysis of plasticizers in PVC tubings**

104 Before performing migration tests, the exact composition of plasticizers present in each PVC tubing
105 was determined by GC-MS after a solvent extraction using the published method described by
106 Bourdeaux et al (6).

107 This analysis allowed us to identify and quantify the main plasticizer present in the PVC matrix as
108 well as the minority ones, which could be found as impurities and could also be released from the
109 devices.

110

111 **Study design**

112

113 **Conditions of the migration assays**

114 Migration assays were performed in the same conditions described by Bernard et al as regard to the
115 choice of the simulant, and of the contact temperature and time (3). Only the flow rate was
116 modified.

117 The used parameters were as follows:

118 - simulant: we chose a 50/50 ethanol/water (v/v) solution which reflects lipid emulsions able to
119 extract plasticizers from PVC medical devices. 3% acetic acid (also proposed in the infusion model)
120 was not selected because the migration appears to be insignificant in it (3).

121 - contact temperature: 25°C was chosen to perform the tests as it corresponds to the ambient
122 temperature most commonly found in adult health care units.

123 - contact time: the infusion tests were performed during 24h in order to mimic the maximal time
124 period of an injectable drug infusion containing lipids.

125

126 **Administration methodology**

127 Based on clinical practices, assays were performed under different flow rates that are usually
128 applied from a syringe pump for the administration of drugs and on infusion sets for gravity
129 administrations. The conditions were the following:

130 - for the tests with extension lines, the syringes were filled with the ethanolic simulant and the
131 extension line was set on the syringe. Then one of the following flow rates was applied during 24
132 hours: 1mL/h, 5mL/h and 10mL/h

133 - for the tests with infusion sets, non-PVC bags were filled with the ethanolic solution and set on the
134 infusion set. Then one of the following flow rates was applied during 24 hours: 8mL/h, 20mL/h,
135 50mL/h and 100mL/h

136 The 8mL/h flow rate was specifically chosen since it is in accordance with the clinical ratio
137 volume/surface of 2L/13dm² recommended in the infusion model of Bernard et al. (all the infusion
138 sets tested in this work have similar inner surface in contact with simulant). The other flow rates
139 correspond to those usually set up in clinical practice: the lower ones with extension lines allow the
140 continuous administration of narrow therapeutic range drugs (e.g amines, anaesthetics, insulin,
141 etc...) whereas the higher ones are used for injectable chemotherapy or antibiotherapy drugs.

142

143 **Kinetic study**

144 In order to study the migration mechanisms, we performed a kinetic study by analysing the
145 cumulated amount of plasticizers released into the simulant at different contact times: 1h, 2h, 4h,
146 8h and 24h. For each contact time, assays were performed in triplicate.

147

148 **Analysis of plasticizer into the simulant**

149 The amount of plasticizers released into the simulant was assessed by gas chromatography coupled
150 with mass spectrometry (GC-MS) (6) after extraction from the simulant. To perform this extraction,
151 600 µl of the ethanolic solution was taken and added to 600 µl of a 2 µg/mL of
152 (benzylbutylphtalate) BBP solution in chloroform. After homogenization (with vortex 20 Hz, 30
153 seconds), the samples were centrifuged (3500 rpm, 5min). Finally, the chloroform phase (below the
154 aqueous phase) was taken for GC-MS analysis.

155

156 As plasticizers are widely present in the environment, to prevent the risk of contamination, the used
157 glass flasks were washed 3 times with chloroform before performing the assays; hemolysis tubes
158 and GC-MS vials were single use.

159

160 **Expression of the results**

161

162 - The initial amount of each plasticizer in the tubing samples was expressed in mass percent (%)
163 (mean ± standard deviation)

164 - Two different approaches were undertaken to verify the impact of the flow rate on the release of
165 the plasticizers:

166 1- a “clinical approach” which gives the amounts of plasticizers able to migrated to patients.

167 The amounts of each plasticizer released into the simulant were expressed in two manners:

168 - the mass (µg) of the plasticizer released into the simulant

169 - this amount was then compared with the initial weight of the PVC sample (mg). It is
170 expressed in mg of migrated plasticizer per 100g of PVC

171 2- a “physicochemical approach” which provides the results of release by standardizing the
172 features of the MD and the volume infused. The migration kinetic was expressed as follow:

173

$$A = \frac{q}{s \cdot v}$$

174

175 A = migration kinetic (µg/dm²/mL)

176 q = quantity of plasticizer released into the simulant (µg) during the migration assay

177 s = area of MD in contact with the simulant (dm²) during the migration assay

178 v = infused volume during the migration assay (mL)

179

180

181 **Statistical analysis**

182 All statistical analyses were performed using Stata statistical software (version 13, StataCorp,
183 College Station, US). The tests were two-sided, with a type I error set at α=0.05. Continuous
184 parameters were expressed as mean ± standard-deviation according to statistical distribution
185 (assumption of normality studied using Shapiro-Wilk’s test). To study longitudinal evolution,
186 correlated repeated data was analyzed using linear mixed models: (1) quantity of plasticizers
187 released during migration assays from the extension lines and from the infusion tests and (2) kinetic
188 of migration of plasticizers. This approach seems more relevant rather than usual statistical tests
189 because assumption concerning independence of data is not met. The (fixed) effects group, time-
190 point evaluation and their interactions time/flow rate were studied. The normality of residuals
191 obtained from these models was analyzed as described previously. Bayesian Information Criterion
192 (BIC) was estimated to determine the most appropriate model, notably concerning the covariance

193 structure for the random-effects due to repeated measures across the time and consequently to
 194 the autocorrelation.
 195 This approach seems more relevant rather than usual statistical tests because assumption
 196 concerning independence of data has not been reach met

197

198 Results

199

200

201 Plasticizers in PVC tubings

202

203 Table 3 shows the nature and the amount of plasticizers in each PVC medical device as analyzed by
 204 GC-MS.

205

206

207 **Table 3** : Qualitative and quantitative composition in plasticizers of the studied medical devices

Type of PVC Medical device	Medical device (MD)	Nature of plasticizer in MD	Quantity of plasticizer in MD (expressed in mass percent)
Extension line	EL n°1 (Cair)	TOTM	31.81
		DEHT	0.06
		DEHP	<LOQ*
	EL n°2 (Codan)	TOTM	30.29
		DEHT	0.05
		DEHP	<LOQ*
	EL n°3 (BBraun)	DEHT	26.74
	EL n°4 (Sendal)	DINP	48.72
DEHP		0.25	
EL n°5 (Cair GM)	DINCH	30.16	
EL n°6 (Cair PM)	DINCH	35.73	
Infusion set	IS n°1	DEHT	37.50
		DINP	34.89
	IS n°3	DINCH	44.27
		DEHP	0.05
	IS n°4	TOTM	40.97
		DEHT	0.15
		DEHP	0.002

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213 Plasticizers migration during infusion: the clinical approach

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215

216 Figures 1 and 2 show the results of the migration assays of the main plasticizers from the 6 tested

217 extension lines and the 4 infusion sets.

218 **Figure 1 : Quantity of plasticizers released during migration assays (3 flow rates tested: 1mL/h;**
219 **5mL/h and 10mL/h – 5 contact times: 1h, 2h, 4h, 8h and 24h) from the 6 extension lines (EL)**
220 **tested. (n= 3; mean +/- standard deviation)**

221
222 **Figure 2 : Quantity of plasticizers released during migration assays (4 flow rates tested: 8mL/h;**
223 **20mL/h; 50mL/h and 100mL/h – 5 contact times: 1h, 2h, 4h, 8h and 24h) from the 4 infusion sets**
224 **tested. (n= 3, mean +/- standard deviation)**

225

226 The quantity of plasticizers released into the simulant raises gradually during the infusion period,
227 regardless the type of device and the plasticizer integrated into the PVC.

228 The amounts of plasticizers released at the end of the procedure (24h) are different according the
229 flow rate: the higher the flow rate, the higher the infused volume and the higher the quantities of
230 plasticizers released, both from infusion sets and extension lines.

231 For examples, by comparing the highest and the lowest flow rates in both migration studies
232 (100mL/h vs 8mL/h with infusion sets and 10mL/h vs 1mL/h with extension lines), the ratios of the
233 amounts of plasticizers released at each flow rate are 6.9 and 8; 3.6 and 2.7; 3.35 and 2.6 and 2.3
234 and 1.7 for TOTM, DEHT, DINCH and DINP respectively.

235

236 Regarding both extension lines of PVC/TOTM, TOTM migration is more important when the device
237 doesn't possess an internal layer of polyethylene. The quantities of TOTM released are about ten
238 times higher than those released from the coextruded extension line, regardless of the flow rate.

239

240 The inner diameter of the tubing does not have any impact on the migration of DINCH. Indeed, the
241 total amounts of DINCH released from the EL5 and the EL6 are quite similar (for an inner diameter
242 of 0.25 and 0.1 cm, respectively) whatever the kinetic time.

243

244 Figures 3 and 4 show the percentages of the initial amounts of DEHT, TOTM, DINCH and DINP
245 having migrated from the extension lines and the infusion sets at 24h as a function of the flow rate
246 set.

247 **Figure 3 : Comparison of the migration of plasticizers from the extension lines at 24h according**
248 **the flow rate (n = 3, mean +/- standard deviation)**

249 **Figure 4 : Comparison of the migration of plasticizers from the infusion sets at 24h according the**
250 **flow rate (n = 3, mean +/- standard deviation)**

251

252 Under identical dynamic experimental conditions, the plasticizers demonstrated different migration
253 abilities within the first 24 h of contact. Regardless the flow rate, DINP and DINCH had the highest
254 degrees of migration in dynamic conditions compared to TOTM and DEHT.

255
256

257 **Plasticizers migration during infusion: the physicochemical approach**

258
259 The figures 5 and 6 show the quantities of the different plasticizers released from the MD expressed
260 by unit area of MD in contact with the simulant (dm^2), by unit volume infused (mL) during the
261 infusion procedure. The application of a lower flow rate may extract more plasticizer at each time of
262 the kinetic, regardless of the plasticizer and the type of device. The findings of statistical analyses
263 reported in tables 4 and 5 are thus consistent except for DEHT from the infusion sets for which
264 results show an important variability.

265

266 **Figure 5 : Kinetics of the plasticizer's migration expressed in $\mu\text{g}/\text{dm}^2/\text{mL}$ from the 6 extension**
267 **lines (3 flow rates tested: 1mL/h; 5mL/h and 10mL/h – 5 contact times: 1h, 2h, 4h, 8h and 24h).**
268 **(n = 3, mean +/- standard deviation)**

269

270 **Figure 6: Kinetics of the plasticizer's migration expressed in $\mu\text{g}/\text{dm}^2/\text{mL}$ from the 4 infusion sets (4**
271 **flow rates tested: 8mL/h; 20mL/h; 50mL/h and 100mL/h – 5 contact times: 1h, 2h, 4h, 8h and**
272 **24h). (n = 3, mean +/- standard deviation)**

273

274 However, except for the non-coextruded extension line (EL2), tables 4 and 5 show that the
275 migration kinetic profiles of each plasticizer are similar at any time, without any significant
276 difference in the interactions between time and flow rate; in other words the variation over time
277 was not significantly different between plasticizers.

278

279 As with the « clinical approach », TOTM migration, expressed in $\text{mg}/\text{dm}^2/\text{mL}$, is different between
280 PVC tubings and PVC/PE tubings. TOTM release is 5 times, 3 times and 2.5 times lower from the
281 coextruded extension line (EL 1) than that from the non-coextruded one (EL 2) at respectively
282 10mL/h, 5mL/h and 1mL/h.

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Table 4 : Statistical analysis of the impact of the flow rate on the migration profile for each plasticizer: (table 4a) study of the interaction time/flow rates and (table 4b) comparisons between flow-rates at any time from the extension lines. Results were expressed as p-values.

290 **Table 4a**

	DEHT	TOTM(EL 1)	TOTM (EL 2)	DINCH (EL 5)	DINCH (EL 6)	DINP
Time/flow rate at time 2h	0.17	0.001	0.04	0.89	0.54	0.49
Time/flow rate at time 4h	0.07	0.20	<0.001	0.63	0.33	0.50
Time/flow rate at time 8h	0.02	0.28	<0.001	0.91	0.29	0.31
Time/flow rate at time 24h	0.05	0.44	<0.001	0.85	0.29	0.01

291
292 **Table 4b**

	TOTM (EL 1)	TOTM (EL 2)	DEHT	DINP	DINCH (EL 5)	DINCH (EL 6)
5mL/h vs 1mL/h	0.125	0.008	<0.001	0.006	<0.001	<0.001
10mL/h vs 1mL/h	0.015	0.001	<0.001	0.005	<0.001	<0.001
10mL/h vs 5mL/h	<0.001	0.040	0.010	0.003	0.392	0.007

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Table 5: Statistical analysis of the impact of the flow rate on the migration profile for each plasticizer: (table 5a) study of the interaction time/flow rates and (table 5b) comparisons between flow-rates at any time from the infusion sets . Results were expressed as p-values.

300 **Table 5a**

	DEHT	TOTM	DINCH	DINP
Time/flow rate at time 2h	0.78	0.47	0.11	0.45
Time/flow rate at time 4h	0.71	0.35	0.43	0.35
Time/flow rate at time 8h	0.70	0.47	0.42	0.30
Time/flow rate at time 24h	0.82	0.87	0.41	0.38

301
302 **Table 5b**

	DEHT	TOTM	DINCH	DINP
20mL/h vs 8mL/h	0.96	<0.001	<0.001	0.44
50mL/h vs 8mL/h	0.13	<0.001	<0.001	<0.001
100mL/h vs 8mL/h	0.05	<0.001	<0.001	<0.001
50mL/h vs 20mL/h	0.27	<0.001	0.02	<0.001
100mL/h vs 20mL/h	0.11	<0.001	<0.001	<0.001
100mL/h vs 50mL/h	0.66	0.02	<0.001	0.95

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311 Discussion

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313 This study has assessed, for the first time, the impact of the flow rate on the migration of
314 DEHP alternative plasticizers from medical devices, using two different approaches that are
315 complementary to characterize this influence.

316 With the clinical approach, the flow rate does influence the migration of all tested
317 plasticizers, by increasing the released plasticizer levels in concordance with an increased infusion
318 rate, leading to higher amounts of plasticizers delivered to the patient after a 24h-period infusion
319 procedure. Each plasticizer has a specific migrability, as demonstrated in our previous work (7): in
320 the same conditions, TOTM was found to have the lowest migration rate, followed by DEHT and
321 then DINCH. We also studied DINP's migration in this study, which is close to that of DINCH: at 24h,
322 respectively 1.10% and 1.67% of initial amounts of DINP had been extracted from the extension line
323 and the infusion set at the highest flow rates of 10mL/h and 100mL/h compared to the 1.50%
324 (bigger diameter) and 0.82% of DINCH found in the simulant. For TOTM and DEHT, the extracted
325 levels were much lower: 0.02% (coextruded line) and 0.14% for TOTM and 0.70% and 0.40% for
326 DEHT at 24h.

327 Comparisons with other studies assessing the migration of plasticizers under dynamic conditions
328 could be performed. Most of them have been carried out with DEHP. In the work of Bagel et al, 3
329 different flow rates were investigated (4): 30, 60 and 90 mL/h. For a same infused volume by
330 extension lines, the authors showed that about 1000 µg of DEHP is released in 8.33h at 30 mL/h,
331 600 µg in 4.17h at 60 mL/h and 500 µg in 2.8h at 90 mL/h. In our study, higher levels of DINP
332 (respectively 17610 µg, 6872 µg and 9961 µg), DINCH (respectively 10060.9 µg, 11285.9 µg and
333 8393.3 µg), and DEHT (respectively 3687.9 µg, 2672.4 µg and 1745.3 µg) were found in the simulant
334 after 8h at 20 mL/h, 4h at 50 mL/h and 2h at 100 mL/h. The quantities of TOTM released were much
335 lower at the same times and speeds: 378.8 µg, 609.1 µg and 489.1 µg. The same comparisons could
336 be performed with the work of Rose et al, showing a 500 µg release of DEHP in a propofol solution
337 and 300 µg in an intralipid solution at 12 mL/h at 24°C during 6h (8). Our results concerning
338 plasticizer migration levels at 10 mL/h after 8h of infusion are the following: 2071.1 µg of DINP,
339 1425.8 µg and 11935 µg (large and small diameter) of DINCH, 632.5 µg of DEHT, 40 µg and 561.6 µg
340 (coextruded and non-coextruded tubing) of TOTM. The amounts of TOTM are even higher after 4h
341 of dialysis session at 500 mL/h (Kambia et al 2001). All this data is consistent with our study to show
342 that the flow rate influences the leaching of all the plasticizers to various degrees depending of the
343 nature of the plasticizer and the simulant. The highest quantities of additives released in the media

344 are observed with highest volumes of simulant infused, whereas the migration is more important
345 with lowest flow rates for a same infused volume. However, data comparison is difficult, because
346 the experimental conditions are not standardized between the studies in terms of nature and
347 volume of simulant, flow rates, contact time, temperature, etc... Moreover, in the field of infusion,
348 two main types of medical devices are used: infusion sets and extension lines that could have a
349 different influence on the release of plasticizers from the PVC matrix. Our work allows this
350 comparison, by assessing in standardized conditions different types of infusion devices made of
351 plasticized PVC, simulating the general clinical practice in adult and pediatric care units. The data
352 collected demonstrates that the flow rate plays a role in the migration of plasticizers. The migration
353 kinetic is higher when drugs are infused at lower flow rates but for a given time period, the greater
354 the flow rate, the higher the level of plasticizer released in the simulant at 24h. This could be easily
355 explained by the volume infused of the simulant. These differences may have important clinical
356 implications: patients receiving such IV therapies may be exposed to variable doses of plasticizers
357 that ideally should remain under the tolerable limit before toxicity, i.e the DNEL (Derived No Effect
358 Level) which represents the human theoretical dose limit. Considering the largest amounts of
359 plasticizers quantified in the simulant at 24h (i.e. at a flow rate of 100mL/h), an inpatient of 70 kg is
360 thus susceptible to be exposed to 0.097mg/kg/d of TOTM, 0.264mg/kg/d of DEHT, 0.77mg/kg/d of
361 DINCH and 0.96mg/kg/d of DINP. For DINP, the obtained value is above the TDI (Tolerable Daily
362 Intake) of 0.15 mg/kg/d of the Danish EPA report (9) For DINCH, the value remains beneath the TDI
363 of 0.15 mg/kg/d of the Danish EPA report or the latest NOAEL limit of 300mg/kg/d for an IV route
364 administration of DINCH given by the work of David et al (10), considering a DNEL of 3mg/kg/d
365 (security factor of 100). However, the exposure dose could be considered as toxic, when compared
366 to the 0.4 mg/kg/d of the NICNAS report (11). For TOTM, as expected, exposure doses are the
367 lowest of all the plasticizers and are far below the TDI of 1.13mg/kg/d (9).

368 Nevertheless, to perform a risk assessment according to the flow rate, the entire infusion
369 therapy should be considered, and not just one infusion procedure per patient. The
370 physicochemical approach could provide information on the specific migration rates of each PVC
371 medical device. The migration kinetic is higher when the solvents are infused at lower flow rates,
372 with major differences between extension lines and infusion sets. The ratios of migration kinetics
373 between the low and the high flow rate for extension lines were of 8 (non coextruded MD) and 2.3
374 (coextruded MD) for TOTM, 2.7 for DEHT, 2.1 and 2.6 for DINCH and 1.7 for DINP.

375 When using the physicochemical approach, the quantities of released plasticizers were
376 compared by MD surface unit and infused volume in order to assess the real impact of the flow

377 rates on the different types and models of our studied medical devices. We showed that there was
378 no significant difference of the migration kinetic profiles depending on the flow rate for a same
379 medical device. Notably, quantities of DEHT released were the same whatever the time of kinetic,
380 which suggests an atypical behavior of the plasticizer.

381 These results highlight that the migration of plasticizers is very variable depending on the type of
382 medical devices:

383 - type and use: the infusion sets are especially used for the administration of high volumes of
384 drug solutions by gravity whereas the extension lines allow a more controlled and precise
385 administration of only tens of milliliters of emergency drugs including some with a narrow
386 therapeutic range. Moreover, the different administration positions (i.e vertical position for the
387 infusion sets and horizontal for the extension sets) may influence the migration by influencing the
388 surface interactions between the plasticizers and the simulant. The results highlight that the
389 migration of plasticizers varies greatly with the type of medical device. Indeed, the quantities
390 released at 24h for a flow rate of 10 mL/h with an extension line made of non-coextruded
391 PVC/TOTM were of 25 $\mu\text{g}/\text{dm}^2/\text{mL}$ whereas they reached 600 $\mu\text{g}/\text{dm}^2/\text{mL}$ at 24h for a flow rate of
392 10mL/h with an infusion set made of non-coextruded PVC/TOTM, i.e a ratio of 24. For the other
393 plasticizers, the same ratios are 18.8; 13.7 and 5 for DINCH, DEHT and DINP respectively.

394 Moreover, a greater variability occurred during the migration assays with infusion sets versus
395 extension lines. The main reason for this is that the flow rate was set up manually for the infusion
396 sets unlike the automatic syringe pump administrations used for the tests using the extension lines.

397 - diameter: the migration kinetic of DINCH is almost 2 times lower when the inner diameter
398 is 2.5 times higher (EL5 vs EL6), although a higher volume of simulant (with the larger diameter of
399 the MD) does finally extract a higher quantity of plasticizer (see result section figure 5). This might
400 be explained by different plasticizer/solvent interactions with the inner surface of the PVC and thus
401 by the matrix penetration of the solvent. Indeed, it has been demonstrated that the storage
402 conditions (i.e the simulant in contact with the PVC surface) could impact the characterization of
403 the surface physico-chemistry, especially during a contact with ethanol. In the work of Salloum et al
404 (12), the infusion MD surfaces are modified and even altered by the solvent during storage. The
405 roughness of the surface, the size and the distribution of cracks on the surface are variable and
406 depend on the type and composition of the MD and the duration of the contact. They showed that
407 it leads to different leaching rates of the additives. In our study, the interactions between the
408 ethanolic simulant and the PVC surface of the two extension lines containing DINCH as main

409 plasticizer are different because of the specific changes on the surface occurring during the assays
410 according the flow rate (different contact time) and the manufacturing process of the MDs.

411 - composition of the PVC matrix: we clearly demonstrated that the polyethylene layer has a
412 protect effect on the migration of TOTM, lowering its migration rate by more than 2 times. As it has
413 already been shown that coextruded extension lines avoid the drug sorption on PVC (4),(13), such
414 devices should be used first in clinical practice. Moreover, all the medical devices tested in our work
415 are composed of plasticized PVC with different initial quantities of plasticizers: extension lines
416 contain 26.7% of DEHT, 31.8% (coextruded) and 30.3% (non coextruded) of TOTM, 30.6% (large
417 diameter) and 35.7% (small diameter) of DINCH and 48.7% of DINP; whereas the infusion sets
418 contain 37.5% of DEHT, 41% of TOTM, 44.3% of DINCH and 34.9% of DINP.

419 These differences should be linked to the higher variability observed with DEHT released from the
420 infusion set. They probably also rely on the specific technicality of the gravity infusion set made of
421 PVC/DEHT (provided by BBraun), although generally, more variability occurred during the migration
422 assays with infusion sets versus extension lines. Moreover, the lower leaching aptitude into oily
423 media of DEHT (i.e ethanolic simulant) compared to other studied plasticizers (14) could have
424 influenced the interactions between DEHT and the simulant. To check this assumption regarding the
425 infusion set supplied by BBraun (Intrafix Safeset), some additional migration assays were performed
426 (see supplementary file n°1). The results confirm a higher variability rate due to the gravity
427 technique (no variability appeared with the same tubing during an infusion with a syringe pump)
428 and furthermore, provided particularly by this infusion set (less variability was observed with
429 another infusion set).

430 Overall, these results suggest that the migration rate is less influenced by the flow rate than
431 by the nature and the composition of the medical device, reflecting complex interactions between
432 the PVC matrix and the simulant, combined with the volume of the infused drug to patient. This
433 may explain a different diffusion ratio for each plasticizer inside the PVC matrix, as it has been
434 demonstrated by Al Salloum et al, by using a coupling Raman confocal microscopy to UV
435 spectroscopy technique (15). We thus recommend that the flow rate be taken into account in the
436 risk assessment of the plasticizers' migration if the tested MD are likely to be used in conditions
437 significantly different in terms of flow rate (which may lead to significant differences in the technical
438 characteristics of tested MD).

439

440

441 **Conclusion**

442

443 This study provides information about the real influence of the flow rate on the migration of
444 plasticizers from PVC medical devices used in infusion conditions. The two approaches developed in
445 our study complementarily characterize this influence. From a clinical view, higher speeds led to
446 higher amounts of plasticizers released to inpatients for a fixed contact time of 24h. On the other
447 side, from a physicochemical view, there was no significant difference of the migration kinetic in
448 relation to the flow rate at each contact point of a same medical device. An increased consideration
449 to the specific features of a medical device should be given, in order to assess patients' exposure
450 risk to alternative plasticizers. The different PVC tubing tested in this study are given as examples
451 and reflect that the risk evaluation should be completed, including all the specific environment
452 parameters. More information could be obtained by profile analyses of the PVC matrix in order to
453 understand specific migration mechanisms according to the composition of the PVC matrix, which
454 could help to develop solutions to prevent these surface interactions.

455

456

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473 References

474

- 475 1. European Union. Regulation (EC) No. 1272/2008 of the European Parliament and of the
476 Council on classification, labelling and packaging of substances and mixtures, amending and
477 repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
478 1272/2008 Dec 16, 2008.
- 479 2. Arrêté du 13 avril 2017 fixant les niveaux de concentration en di-(2-éthylhexyl) phtalate au-
480 dessus desquels l'utilisation de tubulures qui en comportent est interdite en application de l'article
481 L. 5214-1 du code de la santé publique.
- 482 3. Bernard L, Cueff R, Chagnon M, Abdoulouhab F, Décaudin B, Breysse C, et al. Migration of
483 plasticizers from PVC medical devices: Development of an infusion model. *Int J Pharm.* 2015 Oct
484 15;494(1):136–45.
- 485 4. Bagel-Boithias S, Sautou-Miranda V, Bourdeaux D, Tramier V, Boyer A, Chopineau J. Leaching
486 of diethylhexyl phthalate from multilayer tubing into etoposide infusion solutions. *Am J Health-Syst
487 Pharm AJHP Off J Am Soc Health-Syst Pharm.* 2005 Jan 15;62(2):182–8.
- 488 5. European Union. COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on
489 plastic materials and articles intended to come into contact with food. Jan, 2011.
- 490 6. Bourdeaux D, Yessaad M, Chennell P, Larbre V, Eljezi T, Bernard L, et al. Analysis of PVC
491 plasticizers in medical devices and infused solutions by GC-MS. *J Pharm Biomed Anal.* 2016 Jan
492 25;118:206–13.
- 493 7. Bernard L, Cueff R, Bourdeaux D, Breysse C, Sautou V, Group AS. Analysis of plasticizers in
494 poly(vinyl chloride) medical devices for infusion and artificial nutrition: comparison and
495 optimization of the extraction procedures, a pre-migration test step. *Anal Bioanal Chem.* 2015 Jan
496 11;1–9.
- 497 8. Rose RJ, Priston MJ, Rigby-Jones AE, Sneyd JR. The effect of temperature on di(2-ethylhexyl)
498 phthalate leaching from PVC infusion sets exposed to lipid emulsions. *Anaesthesia.* 2012
499 May;67(5):514–20.
- 500 9. The Danish Environmental Protection Agency. Alternatives to classified phthalates in medical
501 devices. 2014. Report No.: 1557.
- 502 10. David RM, White RD, Larson MJ, Herman JK, Otter R. Toxicity of Hexamoll(®) DINCH(®)
503 following intravenous administration. *Toxicol Lett.* 2015 Oct 14;238(2):100–9.
- 504 11. National Industry Chemicals Notification and Assessment Scheme (NICNAS). 1,2-
505 Cyclohexanedicarboxylic acid, 1,2-diisononyl ester ("Hexamoll DINCH"). 2012 Feb. Report No.:
506 EX/170 (STD/1259).
- 507 12. Al Salloum H, Saunier J, Dazzi A, Vigneron J, Etcheberry A, Marlière C, et al. Characterization
508 of the surface physico-chemistry of plasticized PVC used in blood bag and infusion tubing. *Mater Sci
509 Eng C Mater Biol Appl.* 2017 Jun 1;75:317–34.
- 510 13. Bernard L, Cueff R, Breysse C, Décaudin B, Sautou V, Armed Study Group. Migrability of PVC
511 plasticizers from medical devices into a simulant of infused solutions. *Int J Pharm.* 2015 May
512 15;485(1–2):341–7.
- 513 14. Bernard L, Décaudin B, Lecoœur M, Richard D, Bourdeaux D, Cueff R, et al. Analytical
514 methods for the determination of DEHP plasticizer alternatives present in medical devices: A
515 review. *Talanta.* 2014 Nov 1;129:39–54.
- 516 15. Al Salloum H, Saunier J, Tfayli A, Yagoubi N. Studying DEHP migration in plasticized PVC used
517 for blood bags by coupling Raman confocal microscopy to UV spectroscopy. *Mater Sci Eng C Mater
518 Biol Appl.* 2016 Apr 1;61:56–62.

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521 **Supporting information**

522

523 **Figure 1 : Quantity of plasticizers released during migration assays from the 6 extension lines (EL)**
524 **tested** (n= 3; mean +/- standard deviation)

525

526 **Figure 2 : Quantity of plasticizers released during migration assays from the 4 infusion sets tested**
527 **(n= 3, mean +/- standard deviation)**

528

529 **Figure 3 : Comparison of the migration of plasticizers from the extension lines at 24h according**
530 **the flow rate** (n = 3, mean +/- standard deviation)

531

532 **Figure 47 : Comparison of the migration of plasticizers from the infusion sets at 24h according the**
533 **flow rate** (n = 3, mean +/- standard deviation)

534

535 **Figure 58 : Kinetics of the plasticizer's migration from the 4 extension lines** (n = 3, mean +/-
536 **standard deviation)**

537

538 **Figure 69: Kinetics of the plasticizer's migration from the 4 infusion sets** (n = 3, mean +/- standard
539 **deviation)**

540

541 **Table 1: characteristics of PVC tubings from extension lines used in the migration study**

542

543 **Table 2: characteristics of PVC tubings from infusion sets used in the migration study**

544

545 **Table 3 : Qualitative and quantitative composition in plasticizers of the studied medical devices**

546

547 **Table 4 : Statistical analysis of the impact of the flow rate on the migration profile for each**
548 **plasticizer : (table 4a) study of the interaction time/flow rates and (table 4b) comparisons**
549 **between flow-rates at any time from the extension lines. Results were expressed as p-values.**

550

551 **Table 5: Statistical analysis of the impact of the flow rate on the migration profile for each**
552 **plasticizer : (table 5a) study of the interaction time/flow rates and (table 5b) comparisons**
553 **between flow-rates at any time from the infusion sets . Results were expressed as p-values.**

554