Migration of plasticizers from PVC medical devices: Development of an infusion model.

L. Bernard, R. Cueff, MC. Chagnon, F. Abdoulouhab, B. Décaudin, C. Breysse, S. Kaufmann, B. Cosserant, B. Souweine, V. Sautou for the ARMED study groupARMED study group

*CHU Clermont-Ferrand, Pôle Pharmacie, rue Montalembert, 63003 Clermont-Ferrand, France
†Clermont Université, Université d’Auvergne, EA 4676C-BIOSENS, BP 10448, F-63000 Clermont-Ferrand, France
‡Nutox Laboratory, Deritech “Packtox”, INSERM UMR 866, AgroSup Dijon, 1 esplanade Erasme, 21000 Dijon, France
§CHRU Lille, Pharmacie, Avenue Oscar Lambret, 59037 Lille, France
‖ Université Lille Nord de France, EA, CRITA, BP83, 59006 Lille, France
¶Centre de Ressources Technologiques 3Chépas, 63173 Aubière cedex, France
‖ CHU Clermont-Ferrand, Département d’anesthésie-réanimation, rue Montalembert, 63000 Clermont-Ferrand, France
§CHU Clermont-Ferrand, Service de Réanimation Chirurgie Cardiovasculaire, rue Montalembert, 63000 Clermont-Ferrand, France
¶CHU Clermont-Ferrand, Service de Réanimation médicale polyvalente, rue Montalembert, 63000 Clermont-Ferrand, France

1 Abbreviations: TOTM: trioctyl trimellitate; DINP: diisononyl phthalate; DINCH: diisononyl cyclohexane-1,2-dicarboxylic acid; DEHA: bis(2-ethylhexyl) adipate; DEHT: di(ethylhexyl) terephthalate; ATBC: acetyltri-n-butyl citrate.

Abstract
Alternatives to DEHP plasticizers are used in various PVC medical devices (MD) for infusion. As they are able to migrate from these MDs into infused solutions, they may come into contact with patient. Different and specific clinical parameters influence their migration in at-risk situations such as infusion. In contrast to the regulations for Food Contact Materials (MCDA), there is currently no acceptable migration limits for the use of these plasticizers in clinical situations. In order to assess their migration, and thus control the risks linked to these MDs, we developed a migration model for the plasticizers in MDs. To this end, we applied a cross-disciplinary methodological process similar to that used in the food-processing industry, taking into account the MDs’ conditions of use in clinical practice. The simulation model is simple and includes the following conditions: MD should be tested with a dynamic method that respects our established clinical assumption (2L of infused solutions via 13 dm² of plasticized PVC), at a temperature of 25°C and during 24 h of contact, using a 50/50 (v/v) ethanol/water simulant. This model could be proposed as a tool for the safety evaluation of the patients’ exposure risk to plasticizers from PVC medical devices for infusions.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction
The manufacture of medical devices (MD), such as infusion or artificial nutrition tubings, from polyvinyl chloride (PVC) requires the incorporation of plasticizers, which are essential for the flexibility of the MD (Chielinì et al., 2013). However, it is now widely accepted that these plasticizers can migrate from the PVC matrix into infused solutions and thus come into contact with the patient. Yet some of these chemical compounds are likely to present a danger to the patient, as has been demonstrated for diethylhexyl phthalate (DEHP), which has now been classed as a CMR1b risk substance due to its effects on reproduction and fertility. Furthermore, according to article 3 of law 2012–1442, its use in tubings used in pediatric, neonatal, and maternity units will be banned in France from July 1st 2015 if it is present above a certain threshold level that will be determined later by decree (Anon., 2012).

MD manufacturers have replaced DEHP with alternative plasticizers such as TOTM, DINP, DINCH, DEHA, DEHT, or ATBC, based on preliminary toxicological data (Scenihr report (Anon., 2015)) and on physiochemical data that suggests a lower level of migration. However, there still remains some doubts

Corresponding author at: CHU Clermont-Ferrand, pôle Pharmacie, 58 rue Montalembert, 63000 Clermont-Ferrand, Cedex 1, France. Fax: +33 4 73 75 48 29
E-mail address: l.bernard@chu-clermontferrand.fr (L. Bernard).

http://dx.doi.org/10.1016/j.ijpharm.2015.08.033
0378-5173/ © 2015 Elsevier B.V. All rights reserved.
concerning the safety of these plasticizers in MD given the limited number of migration studies carried out under conditions of clinical use (Anon., 2015, 2014).

It is therefore necessary to study this migration in order to assess the exposure of the patients to these plasticizers during the use of the MD in clinical practice. Currently, and contrary to the regulations for Food Contact Materials (MCDA), the harmonized standards (EN ISO 10993) for the biological assessment of MD do not impose acceptable migration limits for additives incorporated into these specific non-invasive class I or invasive MD that do not come into direct contact with the vascular system and are intended for temporary use. It seems necessary to develop a model to assess this migration, to measure and, eventually, to control the risks linked to these MD. Our reasoning was based on existing data in the MCDA field where the migration of additives from the packaging into the contacting food is an assessed risk and has been taken into account for many years, giving rise to restrictions on certain additives. The harmonized European regulation (Regulation CE no. 1935/2004 called the framework regulation (Anon., 2004)) is aimed at ensuring the security of the consumers. A specific standard concerning plastic materials and objects, Regulation EU No. 10/2011 (Anon., 2011), consolidates the text issuing from several guidelines and many amendments. This regulation provided manufacturers with a list of authorized substances along with migration value limits for the compounds present in plastic packaging that is in contact with food, as well as conformity testing that must be applied to assess their migration.

The evaluation process for plasticized PVC MDs can be similar to the one adopted for MCDA by adapting the models to the clinical use of the MD. This process falls within one of the ARMED project’s objectives and consists of assessing the ability of the different plasticizers incorporated into PCV MD to migrate towards

Fig. 1. Methodological process for the setting up of plasticizer migration models for fMDs for infusion.

---

2 ARMED: Assessment and Risk management of MEdical Devices in plasticized polyvinylchloride.
contacting fluids in conditions representative of clinical reality. It involves the setting up of in vitro contact models adapted to the assessment of PVC MD. In the long term, the objective is to determine the migration value limits for the plasticizers incorporated into the PVC medical devices and to propose an acceptable limit for the proportion in the device.

In this article we propose the development of a migration model for the additives in PVC MD during their use in infusions, and more specifically for the alternative plasticizers to DEHP. To do this, we applied a methodological process similar to that used in the food-processing industry, taking into account the MD conditions of use in clinical practice.

2. Materials and methods

2.1. Building of the model

The problem of container/content interactions between the medical device and the contents (drug or administered parenteral nutrition) is partly comparable to that of the interactions existing between the MCDA and food. We created a synopsis of the data available in the food-processing industry that allowed the implementation of the migration tests used. We then transposed this data to the clinical approach of the concept.

The methodology applied to the construction of the infusion models was performed in successive stages. The process is shown in Fig. 1.

Every step of the methodological process, including the final validation of the model proposed, was carried out by a multidisciplinary work group consisting of anesthesiologists, intensive care specialists, clinical pharmacists, engineers, MCDA experts, physico-chemists and material scientists, pharmaceutical form specialists, and toxicologists.

2.1.1. 1st stage: Analysis of reference documents used in the food-processing industry

We began our process with a summary of the reference documents used in the field of MCDA. By focusing on (1) EU Regulation no. 10/2011, which is specific to plastic materials and objects, (2) the migration testing standards described (and allowing for conformity with Regulation no. 10/2011), and (3) the manufacturer’s practical guides for packaging, we identified the key elements describing the models and the current assumptions.

This summary served as a basis for the transposition to the clinical concept.

2.1.2. 2nd stage: identification of the parameters influencing migration in infusion situations

The Scenirh report (Anon., 2015), in association with an analysis of the scientific literature (interrogation of the Medline and SciVerse data base libraries), enabled the identification of parameters likely to influence the migration of plasticizers from MD. These factors were then accurately described using the data from an on-site analysis:

- Contact surface between the materials and solutions in contact: a comprehensive survey of the MD intended for infusion that were commercialized in France in 2014 was carried out in order to determine the characteristics in terms of size (diameter and length of the tubing) and therefore the surface in contact with the fluids circulating in these devices.
- Nature of the contents in contact with the MD concerned: due to the highly varied nature of the injectable drugs and the parenteral nutrition mixtures, a survey of the products used was carried out using professional software (Pharma™, Chিমio™). Their excipient composition was then researched, based on the summary of products characteristics (SCP). This allowed the characterization of the products based in their chemical nature.
- Environmental parameters, conditions of use: the delivery rate and the contact time and temperature were characterized based on the SPC of each drug and on national and international recommendations and consensuses (Chassard and Boulétreau, 1996; Anon., 2005, 2007; O’Grady et al., 2015; Boullata et al., 2014).

2.1.3. 3rd stage: identification of the exposure conditions

We determined the normal conditions of use for these medical devices through their usage in infusion/nutritional assemblies in the health services. We targeted our survey at the “at risk” health services (adult ICU) (Rose et al., 2012; Morton et al., 2013; Anon., 2015)) due to the frequency and the abundance of the infusion acts, whether they are sequential or simultaneous, as well as the nature of the fluids infused. For this last point in particular, our analysis had to be expanded to the adult cancer services (extracting power of excipients from some cancer chemotherapies). Observations were also carried out in the adult ICUs and cancer services at the university hospitals of Clermont-Ferrand and Lille) and were re-read by nursing staff and doctors. They enabled the recreation of the assemblies used and to identify, with the prescriber, the most complex infusion situations employed in the medicinal treatment of patients, i.e., presenting a maximum contact surface between the MD and the infused fluid.

2.1.4. 4th stage: establishment of the clinical assumption

From the clinical data and the data previously collected from the literature, the multidisciplinary work group developed a clinical assumption for the theoretical daily exposure of hospitalized adult patients to the PVC from medical devices. This assumption served as a basis for the design of migration testing models, which allowed a comparison of the migration to the acceptable migration limits in terms of risk (equivalent to the specific migration limits (SML) proposed for the MCDA).

2.1.5. 5th stage: construction of the models

From the data collected and the assumption made, one or more models were proposed, enabling the testing of plasticizer migration from the infusion MD.

2.2. Preliminary migration tests

In order to assess the workability of our model we performed preliminary migration tests with the extension line provided by Cair LGL (Reference PES3301 M, batch number 1SD13T, length 13.5 cm; internal diameter 2.5 mm). The surface of the tubing in contact with the infused solutions was 10.9 cm² and the plasticizer added to the PVC was TOTM.

The amount of TOTM released was analyzed by gas chromatography with mass spectrometry (GC–MS) after liquid/liquid extraction from the simulant. 600 µL of the solution was taken and added to 600 µL of a 2 µg/ml bezylbutylphthalate (internal standard) solution in chloroform. After homogenization (vortex 20 Hz during 30 s), the samples were centrifuged (3500 rpm, 5 min). Finally, the chloroform phase was taken for analysis by GC–MS.

The apparatus consisted of a gas chromatograph coupled to a Clarus 500 mass spectrometer (PerkinElmer, USA). The column used was a 5 Accent Optima (30 m × 0.25 µm 0.25 mmID) (Macherey-Nagel, Germany). The oven temperature increased
from 200 to 300 °C at a rate of 20 °C/min to reach a plateau of 300 °C for 7 min. The temperature of the injector was increased to 300 °C. The temperature of the transfer and the source electron impact lines were maintained at 200 °C. The ionization energy source was 70 eV. The carrier gas flow (helium) was 1.2 ml/min with a leakage flow (split) of 20 ml/min. 1 μL of each sample was injected.

5-point calibration curves were generated with 0.1–25 μg/ml of each plasticizer and 2 μg/ml of BBP. The cubic equation \( y = ax^3 + bx^2 + cx + d \) was used to obtain coefficients of determination \( r^2 > 0.999 \) for all plasticizers. The precision (represented by the coefficient of variation) and the accuracy (represented by the bias) of our method are good as the coefficient of variation is inferior to 10% for all plasticizers. The lower limits of quantification used were 0.1 μg/ml for DEHA, ATBC, the DEHT, and DEHP; 0.25 μg/ml for DINCH; 0.5 μg/ml for the TOTM; and 1.5 μg/ml for DINP.

3. Results and discussion

3.1. Basis of thinking: data from the MCDA

3.1.1. Regulatory and governing standards

The framework regulation n° 1935/2004 [5] (Anon., 2004) defines the inertness principle for packaging intended to be in contact with food, requiring that the packaging must not transfer substances into the food that are likely to present a danger to people’s health.

Regulation 10/2011, specific to plastic materials and objects, sets out a positive list of authorized substances (monomers/additives), as well as the migration limits in food, based on two types of evaluations of the migration phenomenon:

- The overall migration, which represents the maximum authorized amount of non-volatile substances transferred by a material or object to the food simulants. Actually, the usual standard for the MCDA is 10 mg/dm² of material or 60 mg/kg of food simulants; beyond that, the alteration of the foodstuff is considered unacceptable.
- The specific migration of a given component (toxicological criterion), must be such that the migration does not pass the SML (expressed in mg of substance per kg of food) in order to protect the health of the consumer. They are most often calculated from the tolerable daily intakes (TDI).

These regulatory provisions provide the basis on which the manufacturers of plastic packaging verify that the components in their packaging are suitable for contact with food and also to check the conformity of the final product with the requirements of the inertness principle. Furthermore, practical guidelines have been created by the European Commission to help the manufacturers with the performance of the migration tests (Simoneau, 2015) or in the validation of the analytical control methods (Bratinova et al., 2015).

Standards NF EN 1186-1 to 15 (2003) (overall migration) and 13130 1-28 (specific migration (2004, V2)) respectively show the contact conditions for carrying out overall and specific migration tests and also the conditions for the exploitation and delivery of the results (the standards are in the process of being revised).

3.1.2. The migration models used in the case of MCDA

In the field of MCDA, EU Regulation no. 10/2011 specifies the conditions for performing the migration tests. Firstly, these tests can be performed either directly on food or with the help of a simulated food environment (the “simulant”). Additionally, each test must be performed under defined contact and temperature conditions (see paragraphs below) which must reflect, as closely as possible, the future real conditions of use of the tested food packaging, in accordance with the worst foreseeable contact conditions of use during its shelf-life.

The main characteristics that an industrial firm has to take into account in order to perform the migration tests are:

- The simulant is chosen from a predetermined list (see a– below).
- The conditions of the test have to be representative of the future conditions of use of the packaging. Thus, standardized conditions are proposed according to these uses (see b).
- The test should be perform using the suitable validated method proposed by the regulation (see c).

3.2. a – The authorized simulants

A specific list exists of six different simulants to be used in an adequate manner during the simulation tests, based on the type(s) of food(s) intended to be in contact with the food packaging (Table 1). According to the restrictions of the test, substitute simulants (alternative simulants), may be used.

3.3. b – Conditions of the migration tests

Seven standardized conditions have been described (and two extra for simulant E) for the evaluation of overall migration, often represented by the pair “10 days at 40 °C”. For specific migration, the simulation test conditions depend on the foreseeable real use. For predictable very long term contacts specific accelerated simulation conditions may be put in place. Added to this are 2 correction factors to be applied to fatty foods before comparison with the migration limits:

- Reduction factor linked to the fat content (FRF), correcting the specific migration in food containing more than 20% fat, within the limits of its application (infant, etc.),
- correction factor, which takes into account in a conventional way, the greater extraction ability of the fatty food simulant compared to some types of food.

<table>
<thead>
<tr>
<th>Type of food</th>
<th>Simulant*</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic food</td>
<td>10% ethanol</td>
<td>Simulant A</td>
</tr>
<tr>
<td>Acidic food pH &lt; 4.5</td>
<td>3% acetic acid</td>
<td>Simulant B</td>
</tr>
<tr>
<td>Alcoholic food (20%)</td>
<td>20% ethanol</td>
<td>Simulant C</td>
</tr>
<tr>
<td>Alcoholic food ( &gt; 20% )</td>
<td>50% ethanol</td>
<td>Simulant D1</td>
</tr>
<tr>
<td>Lipid emulsion</td>
<td>Vegetable oil(^b)</td>
<td>Simulant D2</td>
</tr>
<tr>
<td>Foods containing free fats on the surface</td>
<td>MPPD modified poly(2,6-diphenyl-p-phenylene oxide) + Tenax(^c)</td>
<td>Simulant E</td>
</tr>
<tr>
<td>Dry and non-fatty foods</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The simulants can be replaced if, based on scientific data, they overestimate the migration compared to the regulatory simulants.

\(^b\) With compositional characteristics.
For example, chocolate is assigned a reduction factor of 5, by which the results of overall migration in simulant D2 will be divided before verifying its conformity with the acceptable limit.

3.4. c – Choice of test method

Based on the type of packaging and its form, the method chosen by a manufacturer to perform the tests can use standardized Calipack® cells, by immersion, filling the object, or in a "sandwich".

It must be noted that the most drastic method is the immersion technique, which imitates a two-sided contact between the plastic packaging and the foodstuff.

3.5. Identification of the parameters influencing migration in an infusion situation

3.5.1. Contact surface between materials and products in contact

Infusions use two main types of plasticized PVC medical devices: the infusion sets, subdivided into set for gravity infusion and electric infusion pump lines, and extension lines. Depending on the manufacturer, each category of devices has its technical and dimensional characteristics. In the construction of our models it was important to characterize the length of the devices (and therefore their surface), as it is a parameter that increases the release of plasticizers (Bagel-Boitlias et al., 2005; Loff et al., 2004) with, according to the authors, the existence of a proportionality relationship. For each device model we calculated the internal surface area likely to be in contact with the circulating fluids that are potential extractors of the plasticizers in the PVC matrix.

Table 2 shows a summary of these characteristics by the category of MD used in infusions.

3.6. Nature of the content in contact with the MD concerned

The analysis of the drugs and products administered by injection enabled the distinction to be made of 4 main types of fluid:

- type 1: fluids that are strongly fatty in nature (parenteral nutrition medications, medicinal fatty emulsions such as propofol),
- type 2: fluids that are weakly fatty in nature (drugs containing Polysorbate 80® based excipients or polyoxyethylene castor oil, such as paclitaxel),
- type 3: fluids that are ionic in nature (drugs containing buffered acid/alkaline mixtures as a base for the excipients. Examples: analgesic such as fentanyl, antibiotics such as vancomycin, injectable anticancer drugs such as irinotecan),
- type 4: fluids that are alcoholic in nature (drugs containing ethanolic excipients such as diazepam).

The data in the literature shows that the fatty nature of the solvents has a considerable influence on the extraction of the plasticizers from the PVC (Bagel-Boitlias et al., 2005; Bagel et al., 2011), with a strength that is comparable to that of ethanol (Jen et al., 2006; Bernard et al., 2014a), thus justifying its use as a simulant. In order to establish our models, it was therefore necessary to check the differences in lipid content of the identified drugs. The data from this analysis of parenteral nutrition mixtures are shown in Table 3.

The parenteral nutrition mixes contain an average of 20% lipid, with little variability between manufacturers. On the other hand, parenteral nutrition by Y-set infusion lines with separated lipids uses pure lipid emulsions consisting of diluted mixtures of different lipid types.

Furthermore, our survey showed pH values ranging from 3 to 12 for the different drugs infused. Yet the effect of pH on the release of plasticizers is not documented in the literature. We therefore tested it by carrying out a few migration tests for DEHP from PVC tubing. These preliminary tests suggest a greater release of plasticizer into solutions with an acidic pH (between 3 and 4) than into those with a neutral of alkaline pH (tested at pH 12). We therefore integrated the pH parameter into the remainder of the work on the development of the migration model.

3.7. The contact conditions between the MD and the fluid in a clinical situation

These conditions include parameters such as the delivery rate and the contact time and temperature.

The flow rates and the duration of the infusion for each injectable fluid were recorded. These two parameters, which are often inseparable, considerably influence the release of plasticizers. The work carried out on DEHP by Loff et al. (2002), Bourdeaux et al. in 2004 (Bourdeaux et al., 2004), and Kambia in 2003 (Kambia et al., 2003) shows that exposure to phthalate increases with the contact time between the PVC container and the contents until the exhaustion of the phthalate in the material. However, the rate of plasticizer migration does not change linearly with time. The study by Bourdeaux et al., carried out on 150 cm extension lines in contact with Polysorbate 80®, showed that the release of plasticizers was very high in the first 24 h then decreased (Bourdeaux et al., 2004). These results are supported by Chellini et al., who demonstrated DEHP release from endotracheal tubings in the early hours of intubation (Chellini et al., 2011). These data was confirmed by Bernard et al. as part of a study to evaluate the efficiency of a protective PVC barrier against this release (Bernard et al., 2014a). The method of administration of injectable drugs varies from one product to another and depends on the indication, the volume to be delivered, the product’s nature, and the profile of the patient. This is why the contact times with the medical devices can vary from a few minutes to 72 h for central lines, and up to 96 h for peripheral lines for non-lipid containing nutrition, which corresponds to the maximum duration of insertion for the infusion set. For injectable drugs containing lipids, the infusion set or the extension line has to be removed every 24 h. In current practice, especially in ICU because of the frequent changing in the daily medication therapy adapted to the unstable clinical situation of the patient, tubings are changed every day at the latest.

In the same way, the extraction of phthalates is encouraged in static situations but the application of an infusion flow does not stop the release process. However, the slower the delivery rate of a solution is, the greater is the amount of DEHP released. Bagel-Boitlias et al., 2005 showed that the accumulated amount of DEHP having migrated after infusion of 250 mL etoposide was 500 mg at

Table 2

Technical characteristics of plasticized PVC medical devices used in infusions.

<table>
<thead>
<tr>
<th>Type of MD</th>
<th>Set for gravity infusion</th>
<th>Electric pump infusion</th>
<th>Extension lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm) [minimum–maximum]</td>
<td>[150–180]</td>
<td>[254–285]</td>
<td>[10–200]</td>
</tr>
<tr>
<td>Internal diameter (mm) [minimum–maximum]</td>
<td>[3–13]</td>
<td>[2.7–3]</td>
<td>[1–2.5]</td>
</tr>
<tr>
<td>Internal surface (cm²) [minimum–maximum]</td>
<td>[141–170]</td>
<td>[254–268]</td>
<td>[3.14–117.8]</td>
</tr>
</tbody>
</table>
90 mL/h and 1000 mg at 30 mL/h. The delivery rates that we identified were highly varied, ranging from 0.1 mL/h (parenteral nutrition in neonatal intensive care services) to 300 mL/h and even 500 mL/h for medicinal infusions that were often short-term, such as analgesics (paracetamol, ketoprofen) or some chemotherapies. 

In contrast to food, there are not multiple thermal conditions of use for infusion medical devices. All administration of injectable drugs, including chemotherapy, is carried out at room temperature, which is around 25 °C in health services. The peculiarity is in the neonatal population, where the use of incubators maintain the conditions reproducing the in utero environment: between 38 °C and 39 °C and with sufficient humidity. Yet it has been shown that temperature favors the release of plasticizers from PVC tubing (Bourdeaux et al., 2004), which could increase by a factor of 20–30% when the temperature rises by 6 °C (Loff et al., 2002). This variable was not considered in the development of our adult model but is a factor to be taken into account for future pediatric models.

All of the clinical data is shown in Table 4.

3.8. Identification of the exposure conditions with infusion

The analysis and comparison of the different infusion assemblies enabled the identification of 3 main infusion routes for injectable drugs. These routes are likely to represent the most unfavorable conditions for exposure to plasticizers as they include the MD used to convey the injectable drugs that are potential extractors, namely parenteral nutrition and other anesthetic/intensive care therapies. We also integrated the issue of iterative daily infusions that lead to the occasional or more frequent changing of the infusion set and therefore an increase in exposure. Taking these “exposing” routes into account allowed us to calculate the overall surface of PVC in contact with the infused fluids. Thus, the PVC surface of each MD included in each route has been calculated based on the MD’s specifications. We found an area of 860.4 cm² for the distal route, 269.7 cm² for the medial route and 156.1 cm² for the proximal route. Cumulatively, it represents a total surface of 12.9 dm², rounded to 13 dm². Fig. 2 is an example of the standard infusion assembly and illustrates a critical health situation in an adult ICU.

3.9. Establishment of the clinical assumption

In adults, based on the food model, the clinical assumption was: “1 adult weighing 60 kg receiving x mL/day of medication administered through x cm² of plasticized PVC tubing.”

In our scenario, the maximum volume infused daily through the “exposing routes” and the surface of the PVC in contact with the fluids administered through these routes should be considered.

To find the daily exposure volume of a patient in an infusion/nutrition risk situation (ICU), our multidisciplinary reasoning led us to consider the nutritional and medicinal volumes infused each day into a patient in the ICU. Our reasoning was based on the French recommendations for the nutritional support of an ICU inpatient and the main infused volumes specified. These current guidelines recommend an energy intake of between 21 and 26 kcal/kg/d for a critically ill patient (Hasselmann and Kummerlen, 2015). For a 70 kg bw patient, this corresponds to an average infused volume of 1500 mL/d. An additional average infused volume of 500 mL has been estimated for injectable drugs (i.e., antibiotics, antifungal agents, analgesics, sedative drugs, pressor amines), some of which exhibit an important plasticizer extraction power. Thus, we considered a global daily infused volume, including TPN and extractable injectable drugs, of 2000 mL.

Patients with serious burns were excluded from the analysis as their infusion volumes are much greater and therefore not representative of all the patients admitted to intensive care.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid composition of the parenteral nutrition products.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of lipid drug</th>
<th>Lipid content</th>
<th>Example of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready-to-use PN mix</td>
<td>“Binary” solutions</td>
<td>Peptamen®, Aminomix®, Olimel®, Perikabiven®, Smofkabiven®.</td>
</tr>
<tr>
<td></td>
<td>Ternary emulsions</td>
<td></td>
</tr>
</tbody>
</table>

Lipid emulsions in vials for PN around 20%

PN: parenteral nutrition.
The non-extractor vascular filling with a very large variability, notably in the acute transitory phase, was not taken into account either in our evaluation of this critical situation.

Taking into account all these considerations, after several working sessions, the multidisciplinary group, which took into consideration the critical scenario principle and referred to an analysis that strictly respected medical practices and recommendations, chose a value of 35 mL/kg/d.

We then defined our adult clinical assumption as “1 adult weighing 60 kg is likely to receive 2 L of medication per day infused through 13 dm² of tubing, which is 1 L of medicinal solution infused per 6.5 dm² of plasticized PVC tubing”.

This assumption will be the basis for determining the Acceptable Migration Limits (AML) for each plasticizer in the medical device into the medium and therefore into the patient. Eventually, it may enable the estimation of exposure, using the Tolerable Daily Intake (TDI) or DNEL (Derived No Effect Level), themselves resulting from experimental data obtained from animals (NOAEL). The TDI represents the tolerated daily dose, i.e., the dose of a product that can be ingested on a daily basis by an individual for the duration of their life without foreseeable drawbacks to human health and based on current knowledge. The safety margin between NOAEL and TDI takes into account:

- the inter-species safety factor, i.e., the potential increased sensitivity of the human physiology to a plasticizer compared to the sensitivity of the animal species tested,
- the inter-species safety factor, considering the physiological diversity within the same species,
- an additional safety factor linked to the variability of the method used.

Consequently, this safety factor between NOAEL and DNEL is often somewhere between 100 and 1000.

The relationship between DNEL and AML for a given plasticizer for a 60 kg man can therefore be expressed as follows:

\[
\text{AML in the medicinal solution (mg/L): } \frac{\text{DNEL (mg/kg/d)}}{2 (L/d)} \times 60
\]

According to our adult assumption, 2 L of medicinal solution are conveyed by 13 dm\(^2\). Thus, the AML can be expressed in mg/dm\(^2\) by dividing the value in mg/L by 13 (Fig. 3).

\[
\text{AML in the medicinal solution (mg/dm}\(^2\): } \frac{\text{DNEL (mg/kg/d)}}{2 (L/d)} \times 13 (\text{dm}\(^2\))
\]

For example, if we consider the TDI of TOTM as 1.13 mg/kg/d ((The Danish Environmental Protection Agency, 2014), the AML of the plasticizer may be expressed as:

\[
\text{AML} = \frac{1.13 \times 60}{2} = 33.9 \text{mg/L, which is } 2.61 \text{ mg/dm}^2
\]

### 3.10. Construction of an infusion model

The results of this methodological process allowed us to put forward a simple simulation model for the migration of plasticizers in infusion/nutrition situations.

#### 3.10.1. Conditions of the models

The common conditions retained for the specific migration model were as follows:

1. Sample preparation: the migration test was performed on MD.
2. Choice of solvent: each MD must be tested with both simulants.
3. 50% ethanolic simulant.
4. 3% acetic acid (simulant for acid-based drugs pH < 4.5).
5. Contact conditions
6. Method for performing the test: the immersion method (the simplest to set up) was not chosen because it is not applicable to multilayered tubing. The open circuit dynamic model was the one chosen.
7. Contact temperature: 25 °C.
8. Choice of contact time: 24 h (if contact between the MD and lipids was expected), otherwise 96 h. Contact occurred over 96 hours with a intermediate sampling after 24 hours.
9. Analysis of the plasticizers in the simulant: at the end of the contact time studied, the quantity of plasticizer released into the simulant was analyzed using a validated separative method with good sensitivity, such as gas phase chromatography coupled to mass spectrometry (Bernard et al., 2015; Lecoeur et al., 2014; Vaccier et al., 2014; Bernard et al., 2014b).

---

**Fig. 3.** Comparison of the MCDA and the MD assumptions (clinical case of an adult in intensive care).
Table 5
Amount of TOTM released from extension sets Cair LGL (ref PES3301 M) at 25 °C into different simulants during 24 and 96 h of infusion.

| Nature of simulant | Contact time (h) | Number of assays | Concentration of TOTM into the simulant (µg/mL) | Total amount of TOTM released from MD (µg) | Total amount of TOTM released per dm² of tubing (µg/dm²) |
|--------------------|-----------------|-----------------|-----------------------------------------------|------------------------------------------|------------------------------------------------|---|
| Ethanol 50%        | 24              | 3               | 1.67 ± 0.42                                   | 34.30 ± 1.57                             | 314.39 ± 14.39                                      |
|                    | 96              | 3               | 1.39 ± 0.19                                   | 108.80 ± 7.9                             | 997.25 ± 72.62                                     |
| Acetic acid 3%     | 24              | 3               | <LOQ*                                         |                                          |                                                 |
|                    | 96              | 3               | <LOQ*                                         |                                          |                                                 |

* LOQ: limit of quantification.

3.11 Dynamic migration tests

According to the validated model, the test parameters were fixed as follow:
- temperature: 25 °C,
- simulant:
  - simulant 1: a mixture of ethanol and water in equal proportions (50/50 v/v),
  - simulant 2: 3% acetic acid,
- contact time: 24 h and 96 h,
- volume infused: 17 mL of simulant infused through the MD (11 cm² of PVC) during 24 h, based on our clinical assumption (2 L of medicinal solution conveyed by 13 dm³).

Each experiment was performed in triplicate for each contact time.

The amounts of TOTM having migrated form the extension lines into the ethanolic solution as a function of time are given in Table 5. No other plasticizer was detected in the simulants, DEHP and DEHT, both common contaminants of TOTM, were undetectable in the solutions after 96 h of contact.

For TOTM, the most important migration was observed after 96 h of contact with the ethanol/water mixture. This situation represents extreme conditions for the plasticizer release insofar as the 50% EtOH/H₂O simulant reflects lipidic emulsions, which are infused for a maximum of 24 h in clinical practice. Even so, the quantity of TOTM released from the extension line at the end of the infusion was below the AML of our proposed model (2.61 mg/dm²) (see Section 3.9).

Moreover, TOTM did not migrate into the acid simulant.

According to our model and the current toxicity data of TOTM, the medical device tested may be considered as safe according to the leaching of plasticizers for infusion use.

This work allowed a specific model to be developed that was adapted for the initial assessment of the exposure risk of patients to plasticizers from PVC medical devices for infusions. Without a standard basis enabling the safety testing of these medical devices with regards to their chemical risk, this model, which results from the transfer of a food-processing industry approach, could be put forward as a tool for the safety evaluation of PVC medical devices. Its development required the implementation of theoretical (complete characterization of the physiochemical properties of the plasticizers and an exhaustive appraisal of their uses) and practical knowledge (experience and clinical expertise in the use of medical devices in infusion and nutritional situations, knowledge of the therapeutic practice of drugs and other fluids in contact with the devices: flow rates, infusion times, changing lines, temperature, etc., and the associated environment). The group work on a multidisciplinary project was essential to obtain a consensus on the parameters required to establish a starting point for the models: the clinical assumption.

This assumption, based on critical situations, was vital for determining the parameters that allowed the elaboration of the migration model and therefore the realization of the comparative tests of the medical devices (determination of the contact surface/infused volume ratio). It is also the element which could allow acceptable migration limits for each studied plasticizer to be proposed, based on the animal toxicity data (NOAEL) and the human theoretical dose limit (DNEL). Otherwise, an adjustment of the composition/formulation of the MD should be considered.

Our preliminary migration tests allowed us to assess the amount of TOTM released from an extension line that is currently used in the ICU, and thus to evaluate the risk in light of the existing toxicological data. This methodology may be applied for the different plasticizers and may allow the risk of exposure related to each PVC medical device for infusion to be assessed.

Our model is given as a proposition. Other migration tests are in progress in order to validated the established parameters on numerous samples. The first results have to be consolidated and more experiments are needed to validate the robustness of this tool before it can be routinely applied.

On the other hand, as with all risk assessments linked to migrating chemical compounds, the determination of the specific migration of each potentially toxic substance must be associated with an estimation of the overall migration for all the migrants present in the specific matrix. In which case, the amount of other additives present in the PVC of the medical devices should be quantified. These other additives could be formulation agents initially present but also non intentionally added substances (NIAS) formed during the manufacturing process of the MD or during its use in clinical practice. This risk assessment is therefore an overall assessment and will allow the “mixing” effects that are due to all the migrating substances to be taken into account.

Finally, a similar methodological process should be adopted with a view to establishing a pediatric model that reflects the conditions of use of MD and therefore the specific exposure of newborns and premature babies. Indeed, these patients are the subject of special attention due to their pathophysiologcal characteristics (notably their enzymatic immaturity and low weight/height ratio), which results in a particularly exposed population, and because of specific clinical parameters such as a higher environmental temperature during the use of PVC MD.

4. Conclusion

Building on a methodology adapted from the MCDA field, our cross-disciplinary task force achieved to develop a simple model reflecting the migration of plasticizers in clinical situations of infusion. This model takes into account the various parameters and clinical conditions that influence the release of the plasticizers from the PVC matrix of medical devices for infusion. After data consolidation, the model could be considered as a tool for the evaluation of the exposure risk of these MDs and acceptable migration limits could finally be proposed.
Further considerations must be done in order to build in a similar evaluation process a pediatric model, a “at high risk of exposure” population.

Acknowledgments

“This study is a part of the project ARMED (Assessment and risk management of medical devices in plasticized poly(vinyl chloride)) which has received the financial support of the French Medicine Agency (ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé)”

The authors wish to also thank the collaborators of the ARMED study group in its task 2 “Migration and transfer analysis” Farida Abdelouhab, Carole Barillon, Lise Bernard, Benoît Boeuf, Daniel Bourdoux, Corinne Bouteloup, Lionel Camilleri, Didier Chassaing, Philip Chennell, Hélène Clauson, Bernard Cosserant, Sylvie Cosserant, Anuay Demazières, Teuta Eljezi, Charlotte Fernandez-Canal, Sylvie Fourgeaud, Sophie Kauffmann, Virginie Larbre, Bruno Pereira, Valérie Sautou, Bertrand Souweine, Mouloud Yessaad (University Hospital, Clermont- Ferrand, France); Bertrand Décaudin, Stéphanie Genay, Morgane Masse (EA GRITA, University of Lille 2, France); Régis Cuff, Emmanuelle Feschet (EA 4676C-Biosens, Auvergne University, France); Gael Grimand, Pierre Pinta (LIOAD UMR 791, University of Nantes) Colette Brysses, Jacques Thébault (Technology Research Centre 35'Inpack, Aubière).

References


The Danish Environmental Protection Agency. Alternatives to classified phthalates in medical devices, Environmental Project No. 1557. (2014).

Scientific Committee on Emerging and Newly-Identified Health Risks, Opinion on the Safety of Medical Devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update).


