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Assessment of targeted non-intentionally added substances in cosmetics in contact with plastic packagings. Analytical and toxicological aspects

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ABSTRACT

Container-content interactions are common in the food and pharmaceutical industries. However, these studies are more complicated in the cosmetic industry, and it is necessary to ensure consumer safety. The objective of this work was to develop a strategy for the toxicological evaluation of leachables for cosmetic packagings. Eleven common plastic packagings were selected to evaluate interactions with 5 simulants (acidic, alkaline and neutral water, 30% and 96% ethanol) chosen to mimic cosmetics behavior. A GC-MS method was developed to screen for 12 non-intentionally added substances of particular concern: 10 phthalates, bisphenol A and distearyl thiodipropionate (European Pharmacopoeia plastic additive 17). Results were analyzed using a toxicological procedure established for this study. Some phthalates and bisphenol A were detected in several samples, but only one contaminant, diisobutyl phthalate (DiBP), was found to be above the set concentration threshold. Using toxicological data, this concentration was found to be safe for users. 96% ethanol appeared to be the strongest simulant in term of extraction, with a maximum concentration of 491 µg/L for DiBP in a 100% styrene-acrylonitrile copolymer packaging. In water simulants, less contaminants were extracted, with concentrations under 20 µg/L.

1. Introduction

Packaging in cosmetics plays an important role firstly for marketing purposes and secondly, and most importantly, for product protection against light or microbiological contamination. The complexity in developing a new packaging relies on the choice of the manufacturing material to have specific properties to achieve its desired functionality in the final type of container. Type of container also has an influence on the ease of use as well as on consumer safety through delivered dose (Gomez-Berrada et al., 2017). A special consideration has to be taken with the different interactions that can exist between the content and packaging more commonly named as container-content interactions (CCI). CCI studies are common in the food and pharmaceutical industries. They highlight the possible migration of molecules from the packaging to the product, which may impact the product quality, efficacy and consumer safety. European legislation has published regulations to define these studies: the European Pharmacopoeia (European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013) for the pharmaceutical industry, regulation EC n°2017/745 for medical devices (European Parliament and Council of the European Union, 2017) and food regulations CE n°10/2011 (European Commission, 2011) and EC n°2018/213 (European Commission, 2018, p. 213) for the food and food contact packaging industries. The cosmetic industry is also concerned *via* cosmetic regulation EC n°1223/2009 (European Parliament and Council of the European Union, 2009). However, in contrast to the two other legislations, this document does not provide thresholds concerning authorized migration limits such as specific migration limits. The only information available for CCI studies are a list of prohibited substances and Article 17 stating that “the non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3”. Article 3 states that “a cosmetic product made available on the market shall be safe for human health […]”. Certain substances are so prohibited when they are deliberately introduced but can be tolerated if they are proved to be non-intentionally added and unavoidable. Annex 1 also attests that the cosmetic product safety report must contain information on impurities, traces and other pertinent facts concerning the packaging material

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Abbreviations

(r)PET	(recycled) PE terephthalate
ADD17	Distearyl thiodipropionate (European Pharmacopoeia plastic additive n°17)
BBP	benzylbutyl phthalate
BMD	benchmark dose
BPA	bisphenol A
CCI	container-content interactions
CMR	carcinogenic, mutagenic and reprotoxic (substances)
COEX	coextruded
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DHP	dihexyl phthalate
DiBP	diisobutyl phthalate
DiPP	diisopentyl phthalate
DMEP	bis(2-methoxyethyl) phthalate
DnBP	di-n-butyl phthalate
DNEL	derived no effect level
DnPP	di-n-pentyl phthalate
EFSA	European Food Safety Authority
EVOH	ethylene vinyl alcohol
GC	gas chromatography
HDPE	high density PE
IS	internal standard
LLDPE	linear low-density PE
LOD	limit of detection
LOQ	limit of quantification
MoS	margin of safety
MS	mass spectrometry
ND	not detected (below the LOD)
NIAS	non-intentionally added substances
NOAEL	no-observed adverse effect limit
PE	polyethylene
PI	packaging item
PiPP	n-pentyl isopentyl phthalate
PP	polypropylene
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RfD	reference dose
SAN	styrene acrylonitrile copolymer
SCCS	Scientific Committee on Consumer Safety
SED	systemic exposure dose
TDI	tolerable daily intake
TTC	threshold of toxicological concern
US EPA	United States Environmental Protection Agency
UV	ultra-violet
XLDPE	cross-linked low-density PE

(purity, stability, etc.). The absence of threshold values and standardized protocols complicates the CCI studies in the cosmetic industry. Nevertheless, CCI studies are legitimate to ensure consumer safety and product conformity and are of increasing interest in this field (Charron et al., 2018).

More than 30% of worldwide plastic production is used for disposable packagings (Thompson et al., 2009). Plastics are the choice materials for packagings because of their ease of use, lightness and low cost. There are more than 30 different plastics used as packaging materials. Moreover, additives are added to plastics to give them specific properties such as greater softness, flexibility or resistance (Bradley and Coulier, 2007; Cao, 2008; Thompson et al., 2009). Additives can be, among others, plasticizers, UV absorbers, antioxidants, dyes or lubricants (Bi et al., 2013; García Ibarra et al., 2018; Lau and Wong, 2000). Because they are not chemically bound to the polymer, they can migrate from the container to the content (Fasano et al., 2012; Gimeno et al., 2012; Hahladakis et al., 2018) and are consequently considered as potential leachables.

Leaching consists of the migration of a compound from the container to its content in normal conditions (leachables) of use or in extreme conditions (extractables). Thus, leachables and extractables can be additives but also non-intentionally added substances (NIAS) (Bignardi et al., 2017; Muncke, 2011). NIAS are compounds that are present in a packaging material but do not have been added for a technical reason. They can be impurities, degradation products or also environmental contaminants (Bach et al., 2012; Lau and Wong, 2000; Nerin et al., 2013).

CCI studies are carried out to monitor leachables and represent important challenges for industries. Trace levels of leachables in complex matrices present a first difficulty in their evaluation. Diesters of 1,2-benzenedicarboxylic acid, commonly known as phthalates, are man-made substances mostly used as plasticizers in plastic materials in order to improve their flexibility (Meeker et al., 2009; Net et al., 2015). They can also be found as impurities in raw materials and can so be considered as NIAS. Used since the 1920s (Net et al., 2015), they have recently come under the spotlight because of their potential hazards and suspected toxicological risks to human health. Indeed, studies have proved that some were endocrine disrupters and/or CMR chemicals (Fabjan et al., 2006; Meeker et al., 2009). Bisphenol A (2,2′-bis(4-hydroxyphenyl)propane) is also known to be an endocrine disruptor and is used predominantly as a starting material to make plastics (Careghini et al., 2015). In Europe, it is prohibited in cosmetic products (European Parliament and Council of the European Union, 2009) and limited in food products (European Commission, 2018, p. 213). Distearyl thiodipropionate is also restricted in Regulation CE N°10/2011 concerning plastic materials intended to come into contact with food; and identified as the seventeenth plastic additive of European Pharmacopoeia (Council of Europe and European Directorate for the Quality of Medicines & HealthCare (EDQM), 2010).

Measuring trace levels of contaminants is a real challenge for analysts, because of the need to attain very low detection and/or quantification limits (In the order of μg/L or mg/L). Therefore, gas chromatography - mass spectrometry (GC-MS) is often used in CCI studies for its sensitivity, in food (Amiridou and Voutsa, 2011; Cacho et al., 2012; Casajuana and Lacorte, 2004; Fasano et al., 2012; Fierens et al., 2012; Guo et al., 2012), pharmaceutical (Gimeno et al., 2014; Jenke et al., 2013; Pan et al., 2008; Roberts et al., 2016) and cosmetic (Chen et al., 2005; Gimeno et al., 2012; Guo and Kannan, 2013; Shen et al., 2007; Thomas et al., 2014) studies. Liquid chromatography is also used, whether it is with UV, fluorescence (Cirillo et al., 2015; Feng and Jiang, 2012; Jenke et al., 2013; Viñas et al., 2015) or mass spectrometric detection (Ferrer et al., 2011; Lateef, 2016; Viñas et al., 2015; Zhang et al., 2016).

Toxicological evaluations are quite complex in the cosmetic industry because of the prohibition of tests on animals since 2009. Plastic materials can contain potentially dangerous substances, such as additives, monomers or NIAS, and toxicologists are responsible for the packaging risk evaluation according to Regulation CE N°1223/2009. Adapted strategies must be developed to overcome these risks and to highlight the importance of controlling cosmetic packagings and their potential contaminants.

Food packagings are prone to leach different types of contaminants depending on the type of food they contain, the temperature, the time of contact; the conditioning surface/volume ratio … In order to avoid the difficulty of analyzing food directly, strategies using simulants have been developed (Bi et al., 2013; Cacho et al., 2012; Fasano et al., 2012) and are listed in the EC 10/2011 ((European Commission, 2011)). Simulants consist of simple matrices such as water, ethanol, olive oil or

alternative simulants and are mimicking the food behavior inside the container. They are easier to analyze, often after an extraction step. In the pharmaceutical industry, simulants can be used too (Jenke et al., 2005; Roberts et al., 2016) but case-by-case studies are often made on each packaging/product couple (Zhang et al., 2016).

The aim of this work was to study selected NIAS based on a pre-established list of potential toxic risks. Inspired by food and pharmaceutical works, a case-study is presented in which 11 potential cosmetic packagings are evaluated and their leachables analyzed using a GC-MS method developed to screen for 10 phthalates (including 9 that are regulated in Europe: benzylbutyl phthalate (BBP), di-*n*-butylphthalate (DnBP), diethylhexyl phthalate (DEHP), diisobutyl phthalate (DiBP), bis(2-methoxyethyl) phthalate (DMEP), di-*n*-pentyl phthalate (DnPP), dihexyl phthalate (DHP), diisopentyl phthalate (DiPP) and *n*-pentyl isopentyl phthalate (PiPP)), bisphenol A and distearyl thiodipropionate (European Pharmacopoeia plastic additive 17) which is regulated by the Regulation CE n°10/2011 (European Commission, 2011). All of these substances are of particular toxicological concern (Thompson et al., 2009).

2. Materials and methods

2.1. Selected packagings

Eleven common cosmetic packagings made up of polyethylene terephthalate (PET), polyethylene (PE), polypropylene (PP) and styrene acrylonitrile copolymer (SAN) were selected from different European suppliers. For three materials (100% PET, 100% PP and COEX 70% PEBDL/30% PEBDR), two sources of packagings were purchased in order to compare the differences between packagings made up of the same materials but originating from different suppliers.

Descriptions of each item are given in Table 1. The surface in contact with the product is calculated according to the shape. This surface corresponds to the surface in contact with the cosmetic formula in a marketed product (*i.e.* at the filling volume indicated in Table 1).

2.2. Chemicals and reagents

For reference standards, benzylbutyl phthalate (BBP, 98%), di-*n*-butylphthalate (DnBP, 99%), diethylhexyl phthalate (DEHP, 99.7%), diethyl phthalate (DEP, 99.5%), diisobutyl phthalate (DiBP, 99%), bis (2-methoxyethyl) phthalate (DMEP, 98.9%), di-*n*-pentyl phthalate (DnPP, ≥99.0%), dihexyl phthalate (DHP, ≥99.0%), bisphenol A (BPA, ≥99%), distearyl thiodipropionate (ADD17, European Pharmacopoeia Reference Standard) and 4,4′-dibromobiphenyl (98%) were purchased from Sigma-Aldrich (St. Quentin Fallavier, France). Diisopentyl phthalate (DiPP, 98%) and *n*-pentyl isopentyl phthalate (PiPP, 99.0% - mixed of isomers) were obtained from Euromedex (Souffelweyersheim, France). *n*-Octadecane (≥99.0%) and absolute ethanol came from VWR (Fontenay-sous-Bois, France) and heptane (99%) from Carlo Erba (Val de Reuil, France).

For simulants, ethanol (96%) was purchased from Cristalco (Chateaubriand, France). Citric acid (≥99.5%) was purchased from Sigma-Aldrich (St. Quentin Fallavier, France). Disodium hydrogen phosphate dihydrate (≥99.5%) and sodium hydroxide (1M) were obtained from VWR (Fontenay-sous-Bois, France). Purified water was obtained from a Merck Millipore Milli-Q system (Millipore, Bedford, MA, USA). Physical-chemical properties, toxicological and regulatory information and the intended use of the studied substances are described in Table 2.

2.3. Migration tests

In the food industry, different simulants are used to mimic contact with different foods. For example, vegetable oil is used to simulate lipophilic products, and acetic acid 3% (w/v) hydrophilic foods (European Commission, 2011). This strategy may also be used for cosmetic studies with an adaptation of the simulants used to mimic cosmetic products. The aim of this method is to define representative simulants capable of creating “worse-case” situations. A large number of cosmetics are oil-in-water emulsions. In these products, the continuous phase exposed to migration is predominantly aqueous. Therefore, water is a useful simulant for cosmetics. In order to be more accurate, three types of water were used: acidic, neutral and alkaline. Acidic water was prepared with citric acid and disodium hydrogen phosphate dihydrate (pH ≃ 4). Alkaline water was prepared with sodium hydroxide solution (pH ≃ 11). Demineralized water was used as the neutral water simulant (pH ≃ 7).

Cosmetic products can also contain alcohol. It is often the case with acne, hair-fixative or fine fragrance products. To simulate these categories of products, ethanol was used at two different concentrations: 96% for products with a high concentration in alcohol and 30% for products with a lower concentration. 96% Ethanol was chosen on the basis of previous experiments performed in the laboratory that showed a higher tendency of most of the studied compounds to migrate to it. Ethanol 30% was also studied in order to control the action of the combination water/ethanol in proportion closer to real cosmetic products.

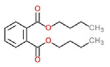
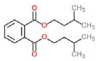
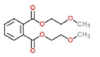
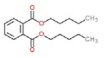
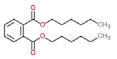
Studied packagings were filled with the different simulants. Volumes were measured with glass measuring cylinders. The bottles were closed by screwing or clipping their respective caps whereas tubes were filled by the top and thermally sealed.

Table 1
Selected packagings and their description.

Code	Material	Appearance	Volume (mL)	Shape and type	Closing system	Theoretical surface in contact with the cosmetic product (cm^2)	Surface/volume ratio
PI1	100% PET	Clear, colorless	100	Elliptical bottle	Cap	124	0.91
PI2	100% PET	Clear, colorless	100	Cylindrical bottle	Cap	115	0.90
PI3	50% PET/50% rPET	Clear, light yellow	200	Elliptical bottle	Cap	209	0.90
PI4	100% PP	Opaque, white	500	Elliptical bottle	Pump	362	0.89
PI5	100% PP	Opaque, dark green	600	Cylindrical bottle	Pump	396	0.86
PI6	100% SAN	Opaque, white	15	Cylindrical bottle	Pump	63	1
PI7	100% HDPE	Opaque, white	100	Cylindrical bottle	Cap	112	0.89
PI8	70% LLDPE/30% XLDPE	Opaque, white	40	Cylindrical tube	Cap	60	1
PI9	COEX 70% LLDPE/30% XLDPE//EVOH	Opaque, white	50	Cylindrical tube	Cap	61	1
PI10	COEX 70% LLDPE/30% XLDPE//EVOH	Opaque, white	50	Cylindrical tube	Cap	66	1
PI11	70% HDPE/30% LLDPE	Opaque, white	40	Cylindrical tube	Cap	59	1

PI: packaging item; rPET: recycled PET; HDPE: high density PE; LLDPE: low linear density PE; XLDPE: cross-linked low-density PE; COEX: coextruded; EVOH: Ethylene vinyl alcohol.

Table 2
Physico-chemical characteristics of targeted compounds.

Compound	Abbreviation	CAS number	Molar mass (g/mol)	Structure	Solubility	Boiling point (Physical state)	Toxicological risk[a]	Use	European legislation	m/z ratios (Stock solution n°)
Benzylbutyl phthalate	BBP	85-68-7	312.37		Water: 2.69 mg/L (25 °C) (1) Soluble in ethanol (2)	370 °C (1) (L)	R1B Endocrine disruptor	Plasticizer (softener) of PVC or other polymers, in sealants, adhesives, paints, inks and lacquers (3)	CE n°10/2011: SML = 30 mg/kg + restrictions CE n°1223/2009: prohibited	91; 104; 149; 150; 206 (solution n°2)	
Di-n-butyl phthalate	DnBP	84-74-2	278.35		Water: 11.2 mg/L (25 °C) (1) Very soluble in alcohol (4)	340 °C (1) (L)	R1B Endocrine disruptor	Plasticizer, solvent for oil-soluble dyes, insecticides and other organics, antifoam agent, textile fiber lubricant, fragrance fixative, insect repellent (4)	CE n°10/2011: SML = 0.3 mg/kg + restrictions CE n°1223/2009: prohibited	104; 149; 150; 205; 223 (solution n°2)	
Diethylhexyl phthalate	DEHP	117-81-7	390.57		Water: 0.34 mg/L (25 °C) (1) Soluble in ethanol (2)	384 °C (1) (L)	R1B Endocrine disruptor	Plasticizer in PVC applications and flexible vinyls (4)	CE n°10/2011: SML = 1.5 mg/kg + restrictions CE n°1223/2009: prohibited	71; 149; 150; 167; 279 (solution n°1)	
Diethyl phthalate	DEP	84-66-2	222.24		Water: 1080 mg/L (25 °C) (1) Miscible with alcohol (4)	295 °C (1) (L)	Endocrine disruptor	Manufacturing celluloid, solvent for cellulose acetate in manufacturing varnishes and dopes, denaturing alcohol, Vehicle for fragrance and cosmetic ingredients (4)	–	76; 105; 149; 150; 177 (solution n°2)	
Di-isobutyl phthalate	DiBP	84-69-5	278.35		Water: 20.3 mg/L (20 °C) (1) Soluble in ethanol (2)	297 °C (1) (L)	R1B	Plasticizer for nitrocellulose, cellulose ether, polyacrylate and polyacetate dispersions. Gelling aid in combination with other plasticizers used for plastic, lacquers, adhesives, explosive material and nail polish (5)	Absent from CE n°10/2011: prohibited CE n°1223/2009: prohibited	76; 104; 149; 150; 167; 223 (solution n°1)	
Diisopentyl phthalate	DiPP	605-50-5	306.40		Insoluble in water (4) Very soluble in ethanol (6)	339 °C (7) (L)	R1B	Plasticizer for nitrocellulose and resin lacquers, preventing foam in manufacturing of glue, in rubber cements (8)	CE n°1223/2009: prohibited	71; 104; 149; 237 (solution n°2)	
Bis(2-methoxyethyl) phthalate	DMEP	117-82-8	282.30		Water: 8500 mg/L (25 °C) (1) Soluble in ethanol (2)	340 °C (1) (L)	R1B	Plasticizer in the production of nitrocellulose, acetyl cellulose, polyvinyl acetate, polyvinyl chloride and polyvynilidene chloride. Solvent, enameled wire, film, high-strength varnish and adhesive, in pesticides (8)	CE n°1223/2009: prohibited	59; 104; 149; 207; 281 (solution n°1)	
Di-n-pentyl phthalate	DnPP	131-18-0	306.41		Water: 0.189 mg/L (25 °C) (1) Soluble in ethanol (2)	342 °C (9) (L)	R1B	Plasticizer in polyvinyl chloride (9)	Absent from CE n°10/2011: prohibited (10) CE n°1223/2009: prohibited	104; 149; 150; 207; 237 (solution n°2)	
N-pentyl isopentyl phthalate	PiPP	776297-69-9	306.41		Water: no available data Soluble in ethanol (11)	371 °C[b] (L)	R1B	Plasticizer in plastic material (12)	CE n°1223/2009: prohibited	71; 149; 219; 237 (solution n°1)	
Dihexyl phthalate	DHP	84-75-3	334.46		Water: 0.24 mg/L (20 °C) (1)	210 °C (5 mmHg) (6) (L)	R1B Endocrine disruptor	Plasticizer for cellulose and vinyl plastics (13)	Absent from CE n°10/2011: prohibited (10)	149; 207; 233; 251; 281 (solution n°1)	

(*continued on next page*)

Table 2 (*continued*)

Compound		Abbreviation	CAS number	Molar mass (g/mol)	Structure	Solubility	Boiling point (Physical state)	Toxicological risk[a]	Use	European legislation	m/z ratios (Stock solution n°)
Bisphénol A	BPA	80-05-7	228.29		Ethanol: no available data Water: 120 mg/L (25 °C) (1) Soluble in alcohol (4)	220 °C (1) (S)	R2 Endocrine disruptor	Monomer used for polycarbonate and epoxy resins (4)	CE n°2018/213: SML = 0.05 mg/kg CE n°1223/2009: prohibited	91; 119; 213; 214; 228 (solution n°2)	
Distearyl thiodipropionate (plastic additive n°17)	ADD17	693-36-7	683.17		Insoluble in water Ethanol: no available data Very soluble in benzene and olefin polymers (14)	MP: 61 °C (6) (S)	–	Plastic additive (15)	CE n°10/2011: SML(t) = 5 mg/kg European Pharmacopoeia	106; 111; 125; 139; 178; 325 (solution n°2)	

References: (1) (Howard and Chemical Rubber Company, 1997); (2) (AFNOR, 2014); (3) (European Chemicals Agency, 2010); (4) (O'Neil and Merck and Co, 2006); (5) (European Chemicals Agency, 2009); (6) (Haynes, 2014); (7) (Environment Agency Austria, 2012); (8) (Federal Institute for Occupational Safety and Health, 2011); (9) (Bureau for Chemical Substances, 2013); (10) (Agence nationale de sécurité sanitaire alimentation, environnement, travail, 2015); (11) (Gimeno et al., 2014); (12) (Federal Institute for Occupational Safety and Health, 2012); (13) (Federal Institute for Occupational Safety and Health, 2013); (14) (Larrañaga et al., 2016); (15) (Council of Europe and European Directorate for the Quality of Medicines & HealthCare (EDQM), 2010).

[a] Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

[b] Data generated by CS ChemProp L: Liquid/S: Solid at atmospheric pressure and ambient temperature; Pressure not specified = atmospheric pressure.

The migration tests strategy is described on Fig. 1. Inert glass containers were used to stock simulants considered as control samples. One was kept at 4 °C and the other in a climatic chamber at 50 °C, in order to verify the effect of heat on the matrices. Moreover, these control samples were used to prove that no contamination had occurred during preparation, emptying and storage steps. This experimental condition permitted an accelerated aging process of the products. Packagings were emptied after storage under accelerated conditions (50 °C/1 month) and kept at 4 °C in order to be sure that the migration is stopped.

55 sets (packaging/simulant) were studied in duplicate. Moreover, 10 blanks were prepared, with 120 samples in total.

Before analysis, simulants in inert-glass containers were removed from the refrigerator and left to come to room temperature, before being transferred to chromatographic vials.

2.4. Analytical procedure

All analyses were performed on an Agilent 7890A gas chromatography system coupled with an Agilent 5975C inert XL MSD with quadripole (Les Ulis, France) equipped with an electron impact ionization source and a Gerstel MPS 2 autosampler. A HP-5MS capillary column (30 m length, 0.25 mm, 0.25 µm film thickness) was used for separation. The temperature of the injector was set to 280 °C. Injection volumes varied depending on the matrix: 1.0 µL was injected for 96% ethanol, 0.8 µL for 30% ethanol and 0.5 µL for aqueous samples. Injection was in split mode (ratio 2:1). Helium was used as a carrier gas at a constant flow of 1 mL/min. The temperature gradient began at 100 °C and was raised to 200 °C at 30 °C/min. Then, the temperature was increased to 280 °C at 5 °C/min and continued at 50 °C/min, until 320 °C (held for 5 min). The temperature of the transfer line and ion source were 250 °C and 230 °C, respectively. The electron impact energy was 70 eV. The compounds were detected in selected ion monitoring (SIM) mode according to m/z ratios presented in Table 2. Dwell time is 50 ms for all compounds except for DMEP and DiPP (25 ms) because 4,4′-dibromobiphenyl is detected in the same m/z window.

Concentration thresholds were determined using regulations (European Commission, 2011; 2018; European Parliament and Council of the European Union, 2009, p. 200), internal data and systemic exposure dose (SED) calculation. The concentration thresholds defined are: 0.5 mg/kg for phthalates, 0.05 mg/kg for BPA and 5.0 mg/kg for ADD17. The analytical method development must therefore attain an LOQ at these values for the corresponding compounds.

Internal standards (IS) are 4,4′-dibromobiphenyl for phthalates, as indicated in the AFNOR norm NF EN 16521 (AFNOR, 2014), and for BPA, since the molecular structures are similar, and *n*-octadecane for ADD17. Individual phthalates, BPA and IS solutions were individually prepared by weighing 10 mg of each compound in 10 mL of absolute ethanol. ADD17 was prepared at the same concentration but with heptane as the dilution solvent. Solid compounds in solvent were placed in an ultrasonic bath for 10 min until complete dissolution. Compounds were separated into two stock solutions (Table 2) in order to avoid too many m/z zones on the same chromatograms and to allow better detection of the peaks. Diluted solutions were prepared to obtain calibration curves for each compound. Dilution solvent varied as a function of the matrix: demineralized water for aqueous simulants; 30% ethanol for 30% ethanol simulant and absolute ethanol for 96% ethanol. 4,4′-dibromobiphenyl and *n*-octadecane stock solutions were added to each solution to obtain final IS concentrations of 500 µg/L and 200 µg/L respectively.

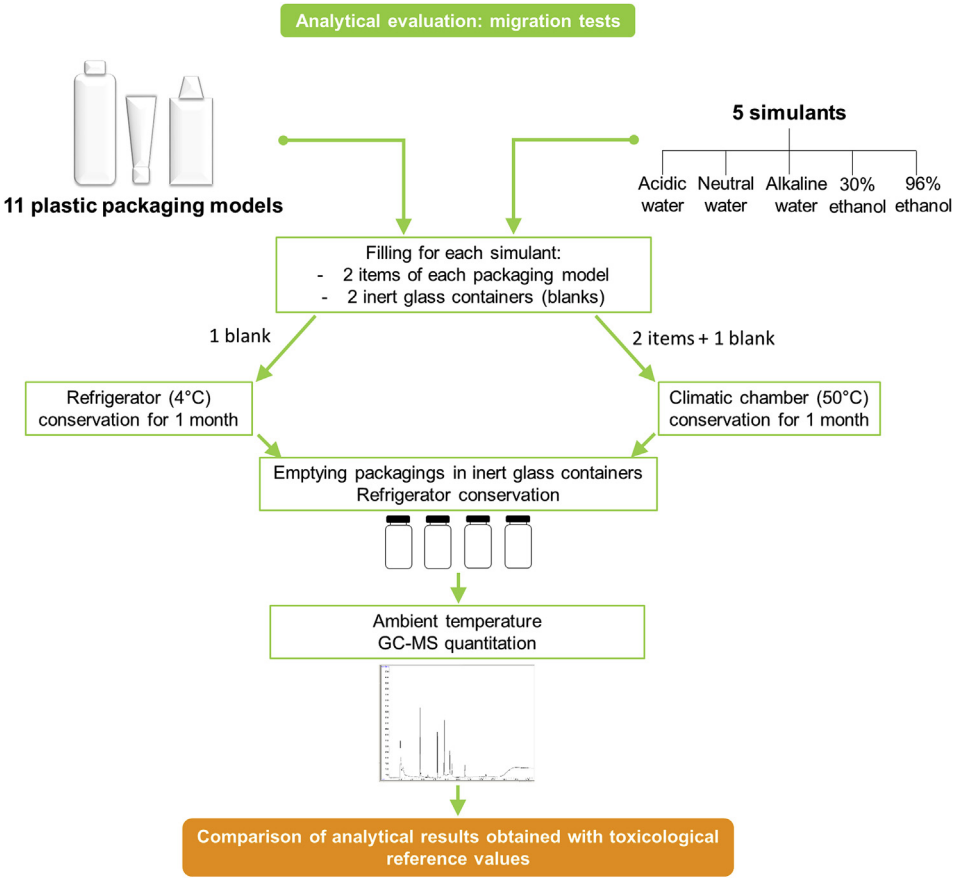


Fig. 1. Workflow of the strategy for migration studies.

2.5. Method validation

LOQs were determined by injecting the lowest concentration solution (in ethanol and in water) until a signal-to-noise ratio of at least 10:1 was obtained for each compound. LODs are considered to be LOQs/3. Linearity was determined by injecting solutions at eight different concentrations from the LOQ. Repeatability is evaluated by injecting six times a solution containing contaminants at the selected concentration threshold. Accuracy is determined by analyzing blanks of absolute ethanol and water spiked at two different levels in triplicate (the selected concentration threshold and twice this value). The recovery is calculated based on Equation (1).

$$\text{Recovery}\ (\%) = \frac{\bar{y}_{exp}}{y_{theo}} \cdot\ 100 \qquad (1)$$

Where $\bar{y}_{exp}$ is an experimental area value obtained by calculating the average of the ratio between compound and internal standard peak areas of 3 replicates. y_{theo} is a theoretical area value obtained from the calibration curve equation, with the concentration of the spiked solutions.

The precision of analysis was estimated by calculating the relative standard deviation of the 3 replicates of spiked samples.

Laboratory control samples (one for each simulant), were analyzed with each set of samples to examine background contamination. A full set of calibration standards was analyzed before each set of samples and control standards were injected during the sets in order ensure system stability. Before each injection set, solvent blank (absolute ethanol, water or 30% ethanol) were injected to ensure the absence of peaks at the retention times of the studied compounds.

In order to confirm that no contamination occurred, control samples were analyzed. If one of the target compounds was detected in a control sample, the control sample peak area was subtracted from the sample peak area.

Validation was performed in absolute ethanol and neutral demineralized water. Parameters were also verified in ethanol 30% in order to be sure that the method is valid in that simulant too.

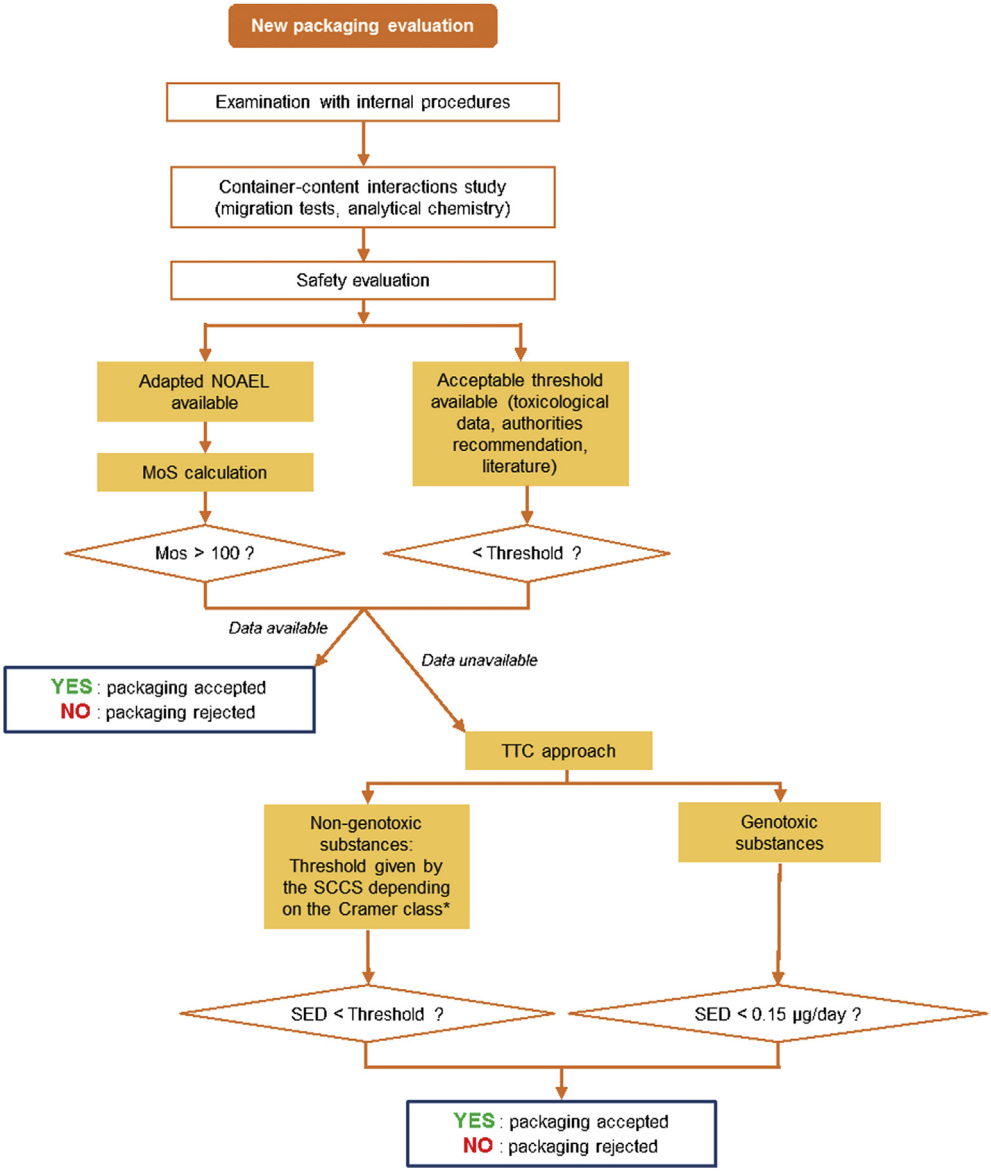


Fig. 2. Workflow of the toxicological evaluation strategy; NOAEL: no observed adverse effect level; MoS: margin of safety; TTC: threshold of toxicological concern; SCCS: Scientific Committee on Consumer Safety; SED: systemic exposure dose. Some other considerations must be taken depending on chemical specificity and according to the TTC concept (*i.e.* organophosphates, carbamates, metals …).

2.6. Toxicological procedure and analysis

The toxicological strategy offers four options for the safety evaluation of different packagings.

Materials and analytical researches combined with toxicological approach were performed to guarantee the compatibility between the container and its content and consequently consumer safety (Fig. 2).

For this purpose, several toxicological values were used: The Tolerable Daily Intake (TDI), the Reference Dose (RfD) and the Derived no Effect Level (DNEL). The TDI is the estimated concentration of a substance which can be ingested daily over a lifetime without significant risks to human health. TDIs are set out by the EFSA (European Food Safety Authority) and are based on selected and appropriate studies. The RfD set out by the US EPA is defined as "an estimate" (with some uncertainties) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Finally, the DNEL (oral or dermal) is defined as the level of exposure to a substance above which humans should not be exposed. All of these values were derived from NOAEL, LOAEL or benchmark dose (BMD) with uncertainty factor for reflection of limited data if necessary. The discrepancies between these different values are due to the fact that US EPA, EFSA and REACH use point of departure values based on different studies, different endpoints and/or different scenarios. As previously explained, different values furthermore arise depending on whether NOAEL, LOAEL or BMD are used, and which safety or uncertainty factors are applied.

Exposure assessment of phthalates was performed using the following information and by considering the worst-case scenario. For this purpose, we considered a total amount of product applied each day equal to 18 g (according to the last version of the SCCS guidance notes–(Scientific Committee on Consumer Safety, 2015)), a total bioavailability equivalent to 100%, a body weight of 60 kg for an adult and only the highest detected concentrations were used for the systemic exposure calculation of each impurity.

3. Results and discussion

3.1. Method performance

The validation parameters are summarized in Table 3. For studied compounds (except ADD17), LOD and LOQ were 2 and 5 µg/L for DEHP and DiBP respectively; 67 and 200 µg/L for DMEP respectively in ethanolic samples. ADD17 values determined only in ethanolic samples were 1333 and 4000 µg/L respectively. In water samples, LOD and LOQ were 2 and 5 µg/L for DiBP to 167 and 500 µg/L for DMEP. These values are comparable to those reported in the literature (Bi et al., 2013; Ferrer et al., 2011; Gimeno et al., 2012; Thomas et al., 2014). Even if there were no pre-concentration steps, LOQ were always smaller than the selected concentration threshold and consequently, the protocol is adapted to the study.

A large linearity ranging from the LOQ to 1000 µg/L was observed for each target compound (to 15000 µg/L for ADD17). Correlation coefficients were greater than 0.990 as recommended by the standardization ISO 12787 (AFNOR, 2011). Repeatability was less than 8% RSD except for ADD17 (13%). The spiking recoveries varied between 90% and 114% for water samples and between 85% and 108% for ethanol samples (96%) and were reproducible as demonstrated by the RSD values which were lower than 10%.

Validation parameters in 30% ethanol were considered as acceptable and are available as supplementary data.

Fig. 3 shows examples of GC-MS chromatograms: (a) a blank of absolute ethanol, (b) a standard solution n°1 in absolute ethanol at the selected concentration threshold and (c) a sample of simulant 96% ethanol after one month in PI8 (70% LLDPE/30% XLDPE).

Table 3
Overview of the method performance characteristics.

Compound		Linear range (µg/L)	Linearity R^2		Repeatability %RSD		Accuracy						LOQ (µg/L) (in water if different)	LOD (µg/L) (in water if different)
							Spiked at concentration threshold			Spiked at twice concentration threshold				
							In ethanol		In water	In ethanol		In water		
			In ethanol	In water	In ethanol	In water	Recovery (%)	%RSD	Recovery (%)	Recovery (%)	%RSD	Recovery (%)	%RSD	
Phthalates	BBP	20–1000	0.991	0.995	3.2	3.8	86	2.8	112	90	4.6	99	5.2	20	7
	DnBP	10–1000	0.996	0.998	1.4	3.6	88	2.5	107	96	0.7	100	2.4	10	3
	DEHP	5–1000	0.991	0.996	2.2	4.6	90	0.9	90	94	1.8	109	2.6	5 (15)	2 (5)
	DEP	10–1000	0.999	0.995	1.4	5.4	92	2.0	94	98	0.8	112	1.0	10	3
	DiBP	5–1000	0.998	0.998	0.7	3.2	96	2.4	96	99	3.9	104	0.7	5	2
	DiPP	10–1000	0.993	0.991	2.8	4.9	85	3.8	104	96	1.4	114	9.9	10 (50)	3 (17)
	DMEP	200–1000	0.992	0.991	1.3	6.0	85	1.7	98	92	0.9	102	2.9	200 (500)	67 (167)
	DnPP	20–1000	0.990	0.993	2.3	5.7	85	2.0	105	96	1.9	111	13.40	20 (30)	7 (10)
	PiPP	10–1000	0.995	0.990	2.5	7.4	92	2.2	114	98	1.2	106	1.9	10 (30)	3 (10)
	DHP	30–1000	0.993	0.991	3.6	5.8	86	2.6	104	93	0.9	111	2.2	30 (80)	10 (27)
BPA		10–1000	0.991	0.997	5.2	6.7	96	0.5	108		0.8	107	3.7	10	3
ADD17		4000–15000	0.991	–	12.7	–	88	24.3	–	108	3.6	–	–	4000	1333

NB: there are no results for ADD17 in water because this compound is in solution in heptane, which is not soluble in water.

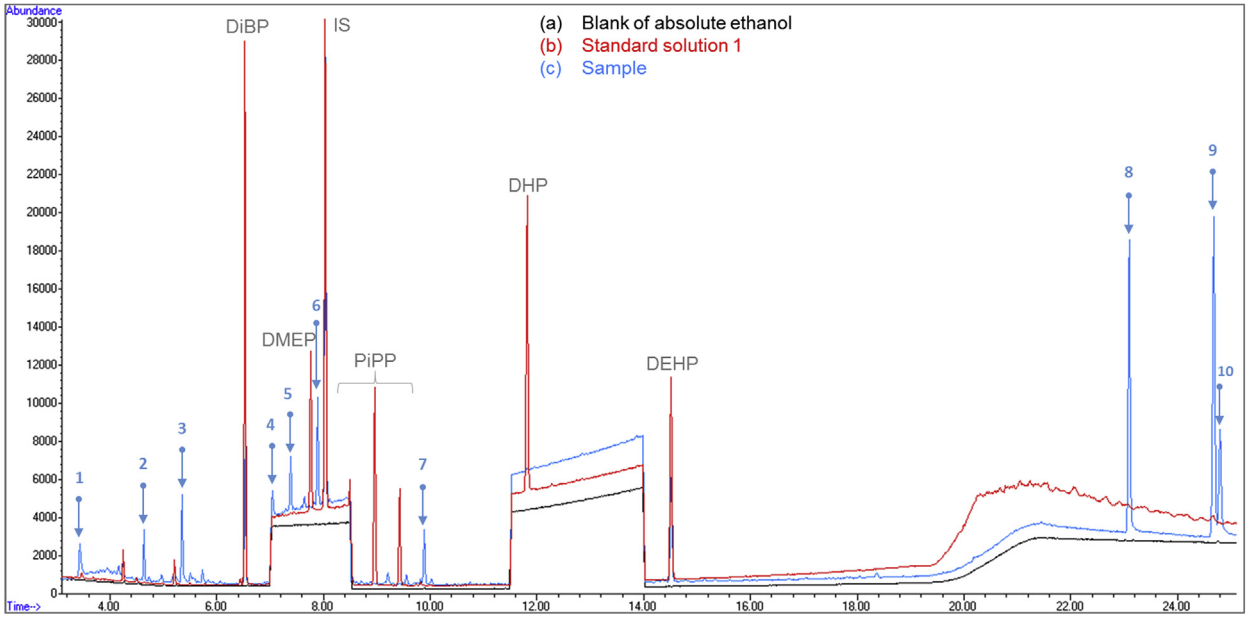


Fig. 3. GC-MS chromatograms in SIM mode obtained from (a) a blank of absolute ethanol, (b) standard solution n°1 in absolute ethanol at selected *concentration* threshold (400 µg/L) and (c) a sample of simulant 96% ethanol after one month in PI8 (70% LLDPE/30% XLDPE) at 50 °C with IS at 500 µg/L. The blue arrows indicate 10 unknown peaks i.e. peaks that are neither phthalates studied nor BPA, ADD17 or IS. The profile in "tread of a stair" is due to evolution of m/z during the analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.2. Migration results

Fig. 4 highlights how many compounds over the 12 studied were detected in each tested packaging. As can be seen on this graph, there are more contaminants detected in PI4 to PI11 than in PI1 to PI3. PI8 (70% LLDPE/30% XLDPE) is actually the packaging with the highest number of target compounds detected (6 out of the 12 studied). On the contrary, in PI3 (50% PET/50% rPET), none of the contaminants were detected (< LOD) whatever the simulant. This packaging can be considered the "cleanest" pack of this study. In several packagings (PI1, PI5, PI7, PI8, PI9, PI10), the total number of contaminants extracted corresponds to the number of contaminants extracted by simulant 96%

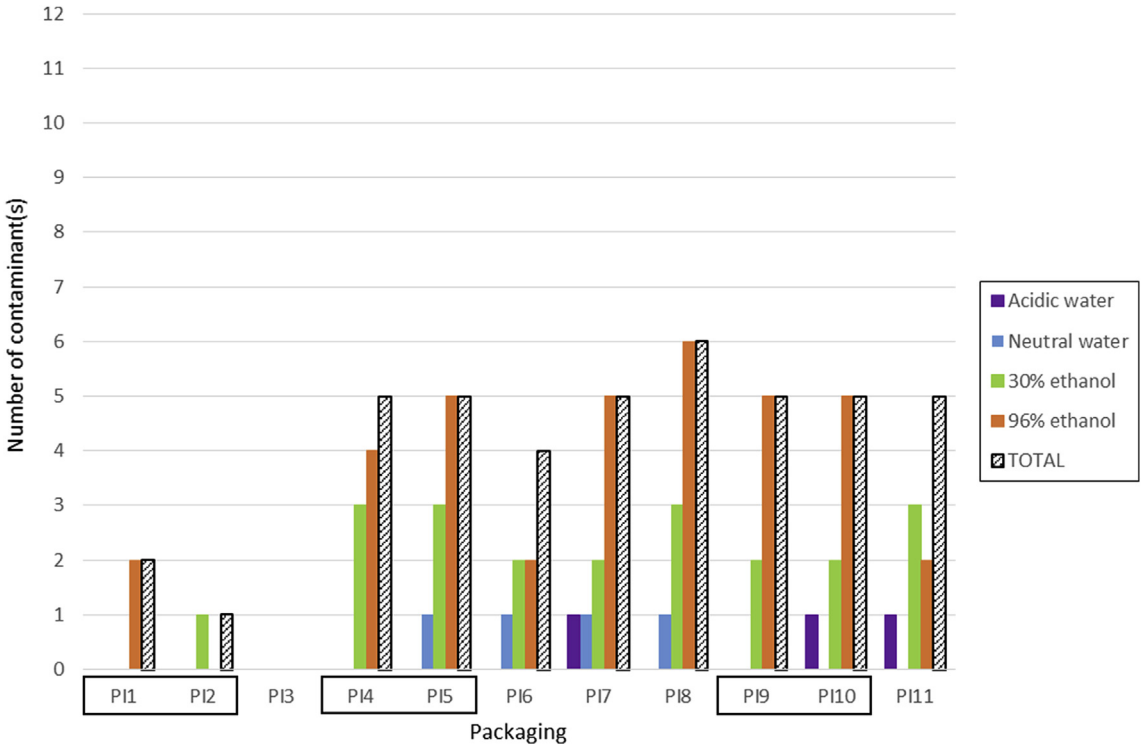


Fig. 4. Number of selected contaminant(s) detected in each packaging reviewed. NB: alkaline water is absent from this graph because none of the studied compounds was detected in this simulant. TOTAL corresponds to the sum of all the different contaminants detected in the packaging in all the simulants. Boxed texts are pairs made up of the same materials but coming from different suppliers (PI1 and PI2 in 100% PET; PI4 and PI5 in 100% PP; PI9 and PI10 in COEX 70% LLDPE/30% XLDPE//EVOH).

ethanol. This is not the case for the other packagings which demonstrate specific behavior versus the simulant type. Both ethanol simulants extracted in 10 packs out of 11, proving that ethanol has the strongest extraction potential of the simulants tested.

Fig. 5 presents the nature of the contaminants detected in each packaging as a function of the simulants used. Five compounds: ADD17, PiPP, DnPP, DMEP and DEHP were not detected at all. Moreover, none of the compounds studied were detected in alkaline water.

An analytical issue occurred during the detection of DEP in acidic water. Actually, at the retention time of DEP, acidic water chromatograms were much disrupted (chromatogram available in supplementary data). Because of this phenomenon, it was not possible to detect DEP in this simulant below 300 µg/L. This concentration is below the selected concentration threshold and this issue was considered as acceptable. Consequently, this contaminant is not represented on Fig. 5a.

DiBP was the only contaminant detected in acidic water (Fig. 5a). Its concentration varied from below the LOQ in packagings PI7 (100% HDPE) and PI10 (COEX 70% LLDPE/30% XLDPE//EVOH) to 20 µg/L in PI11 (70%HDPE/30%LLDPE). This contaminant was detected in only these 3 packagings. In neutral water (Fig. 5b), as in acidic water, only one compound was detected: DEP. It was present in 5 packagings over the 11 studied. The maximum concentration observed was in PI7 (100% HDPE). The contaminants detected in these two simulants are not the same. This observation can be explained by the fact that the concentrations measured were relatively low (close to the LOD/LOQ). Moreover, no data was found on the effect of pH on the solubility of phthalates. It is noticed that none of the compounds studied were observed in packagings PI1 to PI4 and PI9 for the water simulants. The concentrations of DEP and DiBP measured were more than thirty times lower than in 96% ethanol.

In ethanol 30% and 96%, extraction rates were higher, both in terms of the concentrations and number of contaminants detected. In 30% ethanol (Fig. 5c), 4 compounds were extracted. DEP and DnBP were the most frequently extracted compounds detected in 9 packagings out of 11. Their maximum concentrations were measured at 40 µg/L and 7 µg/L respectively. The total concentration varied from below the LOD to 54 µg/L for PI8. This last packaging was the most contaminated, but even with the sum of all compounds, the total concentration is still under the selected concentration threshold of 500 µg/L in this simulant. The higher concentrations were observed with 96% ethanol, in which the sum of the contaminants reached a concentration of 681 µg/L in PI8. BBP and DEHP were the principal compounds extracted. The selected concentration threshold is 400 µg/L in 96% ethanol. The total concentration of contaminants extracted from PI6 and PI8 is above this threshold.

Migration results are exposed in Table 4. Numerical values are given when compounds were detected at a concentration higher than their LOQ. Among the 65 detections, only 35 were above the LOQ. Only DiBP was detected above its selected concentration threshold (500 µg/L in the three water simulants and 30% ethanol; 400 µg/L in 96% ethanol). 491 µg/L (equal to 0.6 ppm) of this contaminant was found in the simulant 96% ethanol contained in the packaging in 100% SAN (PI6). A toxicological evaluation is therefore required in order to determine if this concentration of DiBP presents a risk for consumer safety. DEP was the most detected contaminant, being present in 16 samples. DnBP and DiBP were also found in at least 10 samples.

Comparing the packagings made up of the same materials but coming from different suppliers (PI1 *vs* 2, PI4 *vs* 5 and PI9 *vs* 10), the contamination profiles were not exactly the same. Even if the 100% PET packagings (PI1 and PI2) did not leach the same compounds in the same simulants, they leached very few and very low concentrations of contaminants. On the contrary, PI4 and PI5, the 100% PP packagings leached far more contaminants as with PI9 and PI10 (COEX 70% LLDPE/30% XLLDPE//EVOH). These differences can probably be explained by differences in the quality of the raw materials chosen by suppliers.

This study focused on 12 selected compounds of toxicological interest but also highlighted 10 unidentified compounds (named “unknown peaks 1 to 10” on the chromatogram presented on Fig. 3.) These compounds should be identified to evaluate their toxicological potential and risk for consumers. Although the selected ion monitoring acquisition mode is not dedicated to the identification of molecules, some

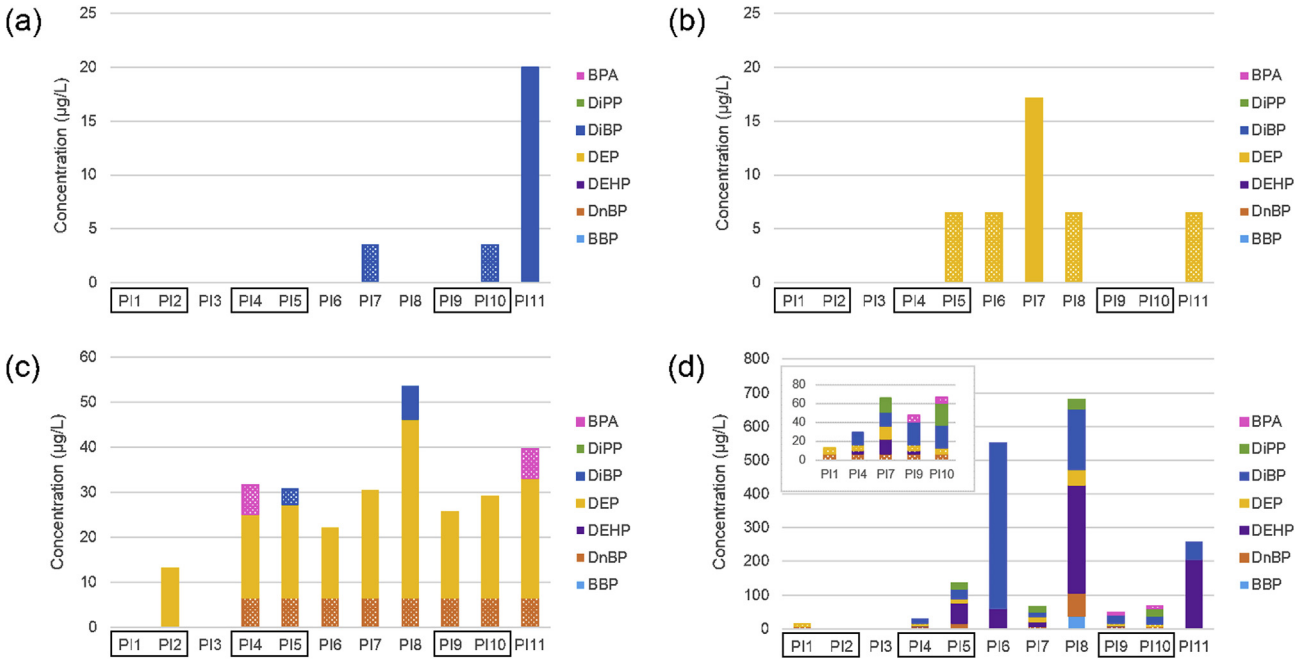


Fig. 5. Total concentration of studied contaminants in each packaging reviewed in (a) acidic water, (b) neutral water, (c) 30% ethanol and (d) 96% ethanol. NB: there is no graph for alkaline water because no target compounds were detected in this simulant. Bars with dots corresponds to concentrations between LOD and LOQ; values for these concentrations were calculated as following: LOD + LOQ/2. Boxed texts are pairs made up of the same materials but coming from different suppliers (PI1 and PI2 in 100% PET; PI4 and PI5 in 100% PP; PI9 and PI10 in COEX 70% LLDPE/30% XLDPE//EVOH). DEP concentration in acidic water (a) is not represented on graph (a) since it is not possible to detect its contaminant under 300 µg/L.

Table 4
Migration tests results in the 5 simulants studied in µg/L.

Simulants	Contaminants	PI1	PI2	PI3	PI4	PI5	PI6	PI7	PI8	PI9	PI10	PI11
Acidic water	Phthalates	DEP: < 300	DEP: < 300	DEP: < 300	DEP: < 300	DEP: < 300	DEP: < 300	DEP: < 300 DiBP: < LOQ	DEP: < 300	DEP: < 300	DEP: < 300 DiBP: < LOQ	DEP: < 300 DiBP: 20.0
	BPA	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
Neutral water	Phthalates	< LOD	< LOD	< LOD	< LOD	DEP: < LOQ	DEP: < LOQ	DEP: 17.1	DEP: < LOQ	< LOD	< LOD	DEP: < LOQ
	BPA	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
Alkaline water	Phthalates	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
	BPA	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
30% Ethanol	Phthalates	< LOD	DEP: 13.1	< LOD	DnBP: < LOQ DEP: 18.6	DnBP: < LOQ DEP: 20.7 DiBP: < LOQ	DnBP: < LOQ DEP: 15.5	DnBP: < LOQ DEP: 23.9	DnBP: < LOQ DEP: 39.8 DiBP: 7.3	DnBP: < LOQ DEP: 19.2	DnBP: < LOQ DEP: 22.6	DnBP: < LOQ DEP: 26.6
	BPA	< LOD	< LOD	< LOD	< LOQ	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOQ
96% Ethanol	Phthalates	DnBP: < LOQ DEP: < LOQ	< LOD	< LOD	DnBP: < LOQ DEHP: < LOQ DEP: < LOQ DiBP: 12.4	DnBP: 16.2 DEHP: 59.8 DEP: 12.5 DiBP: 30.1 DiPP: 17.6	DEHP: 59.5 **DiBP: 491.0**	DnBP: < LOQ DEHP: 15.6 DEP: 14.4 DiBP: 14.5 DiPP: 15.0	BBP: 37.5 DnBP: 69.2 DEHP: 320.7 DEP: 46.2 DiBP: 180.1 DiPP: 27.0	DnBP: < LOQ DEHP: < LOQ DEP: < LOQ DiBP: 24.2	DnBP: < LOQ DEP: < LOQ DiBP: 24.4 DiPP: 53.0	DEHP: 205.9 DiBP: 51.3
	BPA	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOQ	< LOQ	< LOD
	ADD17	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD

Table 5
Toxicological reference values of targeted compounds.

Compound	Abbreviation	TDI (EFSA) mg/kg bw/day	RfD (US EPA) mg/kg bw/day	DNEL dermal (REACH) mg/kg bw/day	DNEL oral (REACH) mg/kg bw/day	Acidic water	Neutral water	Alkaline water	30% Ethanol	96% Ethanol	SED µg/kg bw/day (worst case)	Conclusion
Benzylbutyl phthalate	BBP	0,5	0,2	4,5	0,5	Not detected	Not detected	Not detected	Not detected	Not detected	–	acceptable
Di-n-butyl phthalate	DnBP	0,01	0,1	0,07	0,007	Not detected	Not detected	Not detected	< LOQ	Up to 69,2 (PI8)	0,02	acceptable
Diethylhexyl phthalate	DEHP	0,05	0,02	0,72	0,036	Not detected	Not detected	Not detected	Not detected	Up to 320,7 (PI8)	0,096	acceptable
Diethyl phthalate	DEP	0,5#	0,8	7,5	0,75	< 300	Up to 17,1 (PI7)	Not detected	Up to 39,8 (PI8)	Up to 46,2 (PI8)	0,013	acceptable
Di-isobutyl phthalate	DiBP	ND	–	–	0,008	Up to 20 (PI11)	Not detected	Not detected	Up to 7,3 (PI8)	Up to 491 (PI6)	0,147	acceptable
Diisopentyl phthalate	DiPP	–	–	0,07	0,007	Not detected	Not detected	Not detected	Not detected	Up to 53 (PI10)	0,016	acceptable

a TDI for DEP was not set by the SCF or EFSA, but the TDI of 0.5 mg/kg bw/day was proposed by the World Health Organization (Sekizawa et al., 2003), and may therefore be considered. All other toxicological reference values (TDI, RfD and DNEL) come from the websites of EFSA, US EPA and REACH respectively.

peaks are thought to be related to the phthalate family of compounds. It is well established that phthalate fragmentation under electronic impact mode forms a characteristic protonated phthalic anhydride molecular ion at m/z 149 except for dimethyl phthalate (Jeilani et al., 2011). This is the main ion detected for peaks 1, 2, 5, 8, 9 and 10 and the second one for peak 4. As for DMEP, the latter presents a main peak at 207. No information can be extracted from the mass spectra of the other unknown peaks.

3.3. Toxicological analysis of results

The results obtained were compared to the toxicological reference values (results are presented Table 5). Because the following compounds BBP, DMEP, DnPP, PiPP, DHP, BPA and ADD17 were not detected (whatever the pack and simulants used), assessment cannot be performed. For the other impurities (DnBP, DEHP, DEP, DiBP and DiPP), calculated SED were 0,02, 0,096, 0,013, 0,147 and 0,016 µg/kg bw/day respectively: all of these values were always below the reference values used (expressed as mg/kg bw/day) as well as the TTC value. Moreover, it should be noted that these impurities are found preferentially with the simulant ethanol and more precisely with 96% ethanol. In view of such low exposures of these impurities found in the samples, there would be no quantifiable risk for the consumer.

4. Conclusion

Cosmetic products are used on a daily basis by adults, teenagers but also children and babies. Exposition to plastic additives through the use of hygiene or beauty products must be controlled and evaluated to ensure consumer safety.

A strategy developed to evaluate new packagings through the analysis of 12 toxicologically selected compounds were presented. This work combines analytical chemistry and toxicological evaluation and aim to be a base for developing a model applicable to all the NIAS. Eleven packagings were put in contact with 5 simulants chosen to mimic cosmetics behavior in order to reinforce the safety evaluation of the cosmetic containers. Some phthalates and BPA were detected in several simulants but without any risks for consumers. DiBP and DEHP were detected at high concentrations compared to the chosen concentration threshold. However, these quantities were proved to be safe for users.

A more exhaustive study could be led to identify other molecules of toxicological interest. Screening studies would enable an extension of the studied compounds panel.

The analytical method presented in this paper could be associated with suitable extraction techniques to extend the study to oily simulants such as liquid paraffin or glycerin. These matrices would allow to cover a larger panel of cosmetic products, since they are close to water in oil emulsions or formulas with high contents of glycerin or liquid paraffin. Moreover, the leaching of phthalate is probably accentuated because of their lipophilic profile.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.030.

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