Talanta 129 (2014) 448–458

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Review

Analytical methods for the determination of personal care products in human samples: An overview

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ARTICLE INFO

Article history:
Received 19 February 2014
Received in revised form
22 May 2014
Accepted 28 May 2014
Available online 6 June 2014

Keywords:
Personal care products
Preservatives analysis
Benzophenone UV-filters analysis
Antimicrobials analysis
Musk fragrances analysis
Sample preparation

ABSTRACT

Personal care products (PCPs) are organic chemicals widely used in everyday human life. Nowadays, preservatives, UV-filters, antimicrobials and musk fragrances are widely used PCPs. Different studies have shown that some of these compounds can cause adverse health effects, such as genotoxicity, which could even lead to mutagenic or carcinogenic effects, or estrogenicity because of their endocrine disruption activity. Due to the absence of official monitoring protocols, there is an increasing demand of analytical methods that allow the determination of those compounds in human samples in order to obtain more information regarding their behavior and fate in the human body. The complexity of the biological matrices and the low concentration levels of these compounds make necessary the use of advanced sample treatment procedures that afford both, sample clean-up, to remove potentially interfering matrix components, as well as the concentration of analytes. In the present work, a review of the more recent analytical methods published in the scientific literature for the determination of PCPs in human fluids and tissue samples, is presented. The work focused on sample preparation and the analytical techniques employed.

Contents

1. Introduction

Personal care products (PCPs) comprise different groups of compounds that are currently used as additives in different common products such as cosmetic, household, food or pharmaceutical

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http://dx.doi.org/10.1016/j.talanta.2014.05.052
0039-9140/

products, among others. Considerable amounts of PCPs are used in everyday human actions, so they are produced in large quantities (thousands of tons per year). Although these compounds are used in some products intended for direct ingestion, the main route of exposure is the absorption through the skin, being further metabolized and eventually bioaccumulated and/or excreted [1–3]. This dermal absorption may result in adverse health effects as dermatitis but also in more serious effects, such as mutagenic, carcinogenic and estrogenic activity [4–7]. Because of their adverse effects on human health and their potential bioaccumulation, PCPs are regarded as emerging organic contaminants [8]. The development of accurate methods for simultaneous determination of more than one group of these contaminants and their degradation products, which in some cases are more harmful that the parents compounds, in human fluids (urine, plasma, breast milk or semen) or tissues (adipose tissue, placenta), is consequently of major interest. As a result of this growing need for analytical methodologies, in recent years there has been a notable increase in the publication of validated analytical methods concerning to the determination of different PCPs in human samples.

Regarding experimental issues, due to the complexity of the biological matrices and the low concentration levels of these compounds in samples, certainly it is of essential importance the optimization of new sample treatment procedures. In this way, a sample clean-up to remove the interference of matrix components in the analysis and stages for concentration of analytes, are both required to achieve a selective and sensitive determination of PCPs in human samples. Although the most widely analyzed matrix is urine, other more complex samples, such as placental tissue, have also been analyzed [9–11].

The validation of single methods for multiresidue analysis of different families of those compounds is convenient, since it would reduce the overall analysis time, field sampling and total costs. Moreover, comprehensive information about multiple classes of PCPs is required for risk assessment studies, since chemicals may interact to yield synergic toxicity effects on exposed organisms [12].

In this context, the aim of the present review is to provide a comprehensive overview of the recent developments related to the determination of PCPs in human fluids and tissues, with special emphasis on sample preparation and analytical techniques as well as the achieved detection limits (LODs).

2. Personal care products

The PCPs selected for review in the present work belong to four different chemical families: preservatives; antiseptics/disinfectants; benzophenone UV-filters and fragrances. These compounds were selected based on production/usage, toxicity and potential hormonal activity.

2.1. Preservatives

A preservative is a substance that is added to final products such as personal hygiene products, foods and beverages, pharmaceuticals, wood, biological material, etc., to prevent decomposition by microbial growth or by undesirable chemical changes. Parabens (PBs), the alkyl esters of *p*-hydroxybenzoic acid, are widely used for this purpose, especially against mold and yeast. Methylparaben (MPB), ethylparaben (EPB), propylparaben (PPB), butylparaben (BPB) and benzylparaben (BzPB) are the most commonly used compounds, and individually or in combination, they are used in over 13,200 different commercial formulations [13]. The widespread use of parabens arises from their low toxicity, broad inertness, worldwide regulatory acceptance and low cost. However, nowadays there is an increasing trend to avoid using parabens because of growing evidence that they act as endocrine disrupters [14,15].

2.2. Antiseptics/disinfectants

Antiseptics are antimicrobial substances that are applied to living tissue/skin to reduce infections, sepsis or putrefaction. Antiseptics are generally distinguished from disinfectants, which destroy microorganisms found on non-living objects. Because of their properties, antiseptics and disinfectants are widely used in PCPs, thus, they are common ingredients in soaps and cosmetics. Triclosan (TCS) and triclocarban (TCC) are the most commonly used. In Europe about 350 t of TCS are produced annually for commercial applications [16]. Nowadays, concerns have been raised about them because of their pronounced microbial and algal toxicity, and their potential for fostering antimicrobial resistance [17,18].

2.3. Organic UV-filters

Organic UV-filters are often used to protect skin against UV radiation damage. They are constituents of many daily products such as skin creams, body lotions, hair sprays, hair dyes, shampoos and sunscreen. The European Union (EU) Regulation 1223/2009 – Cosmetics Regulation – provides a robust, internationally recognized regime, which reinforces product safety. It stipulates the compounds that are able to be used as UV-filters in cosmetics and their maximum concentrations [19]. The family of benzophenones (BPs) is one of the most frequently used groups of UV-filters. BPs consists of 12 main compounds, called from benzophenone-1 (BP-1) to benzophenone-12 (BP-12), as well as, other less known as 2-hydroxybenzophenone (2-OH-BP), 3-hydroxybenzophenone (3-OH-BP) and 4-hydroxybenzophenone (4-OH-BP). Other important families of UV-filters widely used are *p*-aminobenzoic acid and its derivatives, camphor derivatives, salicylates, methoxycinnamates and benzimidazoles. Despite their widespread use, there is increased concern about some of these compounds because of their possible estrogenic activity [20,21]. Because most of these compounds have been carefully studied in a recent review paper published by Chisvert et al. [22], the majority of them have not been studied in the present review. However, BPs are included since the cited review only develops the determination of benzophenone 3 and 4 as target compounds in biological fluids and it has been estimated that it is important to complete and expand the valuable information provided.

2.4. Musk fragrances

Synthetic musk fragrances (SMs) have been widely used to replace the natural ones and they can be found in a large amount of manufactured products such as laundry detergents, softeners, soaps and cosmetics. The main groups of SMs are nitro and polycyclic musk compounds. The most commonly used nitro musks are musk xylene (MX) and musk ketone (MK) whereas musk ambrette (MA), musk moskene (MM) and musk tibetene (MT) are less frequently used [23]. The use of nitro musks is being limited due to their environmental persistence and potential toxicity to aquatic environments [24]. Polycyclic musks are currently used in higher quantities than nitro musks being celestolide (ADBI), galaxolide (HHCB) and toxalide (AHTN) the most commonly used and traseloide (ATII), phantolide (AHMI) and cashmeran (DPMI) less usual. However, some polyciclic musks are being studied because of they are suspected to act as selective estrogen receptor modulators [24].

3. Analytical methods for PCPs determination in human fluids and tissues

If we classify research works dealing with the determination of PCPs in human samples according to the studied matrix (Tables 1–3), it can be easily observed that urine, followed by blood are the most usually studied human matrices. Other matrices such as milk, semen or placenta tissue have been much less analyzed.

To date, the most analyzed PCPs are the preservatives MPB, EPB, PPB and BPB; the antiseptic TCS; the UV-filter BP-3 and the musk fragrances HHCB and AHTN. TCC, 4-MBC, MK or MX have

Table 1
Analytical methods for the determination of PCPs in urine.

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
BP-3	– Enzymatic hydrolysis with β-glucuronidase	LC-UV	No data	Total content	[25]
BP-1, BP-3, BP-8	– SPME (direct immersion)	GC–MS (EI)	5–10 ng mL^{-1}	Free forms	[26]
BP-3	– Acid hydrolysis with HCl – SPE (C18)	LC-UV Vis	No data	Total content	[27]
BP-3 MPB, EPB, PPB, BPB	– Enzymatic hydrolysis with β-glucuronidase – SPE (C18)	LC-MS/MS (ESI)	0.20 ng mL^{-1} 0.09–0.30 ng mL^{-1}	Total and free form content	[28]
BP-3	– Enzymatic hydrolysis with β-glucuronidase – Add ACN and centrifuge	LC-UV	0.08 μg mL^{-1}	Total content	[29]
BP-3 TCS	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	0.3 ng mL^{-1} 2.0 ng mL^{-1}	Total and free form content	[30]
BP-3	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	0.5 ng mL^{-1}	Total and free form content	[31]
PBs	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	0.10–0.18 ng mL^{-1}	Total content	[32]
PBs BP-3 TCS	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	0.10–0.18 ng mL^{-1} 0.3 ng mL^{-1} 2.0 ng mL^{-1}	Total content	[33]
MPB, EPB, PPB, PBP, BzPB, BP-1, BP-2, BP-8, 4-OH-BP TCS and TCC	– Enzymatic hydrolysis with β-glucuronidase – LLE (ethyl acetate)	LC-MS/MS	LOQs: 0.2–1.0 ng mL^{-1} 0.7–2.0 ng mL^{-1} 0.5 ng mL^{-1}	Total content	[34]
MPB, EPB, PPB, BPB BP-3 TCS	– Enzymatic hydrolysis with β-glucuronidase – SPE (C18)	HPLC-MS (APCI)	0.2–0.5 ng mL^{-1} 0.2 ng mL^{-1} 0.1 ng mL^{-1}	Total content	[35]
BP-3	– Filter sample and adjust pH (2) – SDME (25 min)	LC-UV	1.3 ng mL^{-1}	Free form	[36]
TCS	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	2 ng mL^{-1}	Total and free form content	[37]
BP-1 BP-3	– Centrifuge – Enzymatic hydrolysis with β-glucuronidase/ arylsulfatase – SPE (C8)	LC-UV	2 ng mL^{-1} 40 ng mL^{-1}	Total and free form content	[38]
BPB	– Enzymatic hydrolysis with β-glucuronidase – SPE (Strata-X) in an automated system	LC-MS/MS (ESI-)	0.3 ng mL^{-1}	Total content	[39]
TCS	– enzymatic hydrolysis with β-glucuronidase/sulfatase – SBSE and TD	TD-GC–MS (EI)	0.05 ng mL^{-1}	Total and free form content	[40]
BP-3	– Lyophilize sample – Dissolve in MeOH:H_2O (9:1, v/v) and centrifuge	LC-UV	3.9 ng mL^{-1}	Free forms	[41]
BP, BP-OH, 2-OH-BP, BP-3, BP-10	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – SBSE (60 min) and TD	GC–MS (EI)	0.005–0.010 ng mL^{-1}	Total content	[42]

Table 1 (*continued*)

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
TCS	– Hy-LLE-Ac (acetylation) – Hy(acid hydrolysis)-SPE-Ac – Gluc (enzymatic hydrolysis)-SPE-Ac – Gluc-ExMe (extractive methylation)	GC–MS (EI)	Qualitative	Total content	[43]
BP, BP-OH, BP-3, BP-10	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – HF-LPME (15 min)	GC–MS (EI)	0.005–0.01 ng mL^{-1}	Total content	[44]
MPB, PPB, BPB BP-3	– Enzymatic hydrolysis with β-glucuronidase – On-line SPE (C18)	LC-MS/MS (APCI-)	0.2–1.0 ng mL^{-1} 0.4 ng mL^{-1}	Total content	[45,49]
BP-1, BP-3, BP-8, BP-2, 4-OH-BP	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – LLE with methyl tert-butyl ether/ethyl acetate	LC-MS/MS (ESI-)	0.082–0.28 ng mL^{-1}	Total content	[46,57]
BP-3 BP-4	– Filter sample and adjust pH (6.0) – On-line SPE (DEA)	LC-UV	60 ng mL^{-1} 30 ng mL^{-1}	Free forms	[47]
BP-1, BP-3, BP-8, THB	– Filter and enzymatic hydrolysis with β-glucuronidase/sulfatase – Add formic acid (pH 3) – SPE (C18)	LC-MS/MS (ESI+)	0.027–0.103 ng mL^{-1}	Total content	[48]
PBs	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – Automated SPE (Stracta XL)	LC-MS/MS (ESI-)	0.07–0.40 ng mL^{-1}	Total content	[50]
TCC + 2 metabolites	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Add formic acid and centrifuge – On-line SPE (C18)	LC-MS/MS (ESI-)	0.10 ng mL^{-1}	Total and free form content	[51]
TCC + 2 metabolites	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Dilute with Milli-Q water and centrifuge – On-line SPE (C18)	LC-MS/MS (ESI-)	0.10 ng mL^{-1}	Total content	[52]
TCS	– Mix with ACN and centrifuge – Dilute with deionized water – UAEM-SFO with 2-dodecanol	CE-UV	0.01 ng mL^{-1}	Free form	[53]
TCS	– Adjust pH (7) and Filter – SPE (Oasis HLB) – MAD with BSTFA-1% TMCS	GC–MS (EI)	0.6 ng mL^{-1}	Free form	[54]
TCC	– Acid hydrolysis with HCl – Neutralize with NaOH mixed with acetic acid – LLE with ethyl acetate and centrifuge	ELISA	LOQ 10 ng mL^{-1}	Total content	[55]
TCS	– Dilute with water and Filter – SBSE and desorption with CAN	LC-DAD	LOQ 10 ng mL^{-1}	Free form	[56]
MPB, EPB, PPB, BPB, BzPB, HepPB	– Enzymatic hydrolysis with β-glucuronidase – LLE with ethyl acetate	LC-MS/MS (ESI-)	LOQs 0.02–0.03 ng mL^{-1}	Total content	[58]
MPB, EPB, PPB, BPB TCS	– Enzymatic hydrolysis with β-glucuronidase – On-line SPE (C18)	LC-MS/MS (APCI-)	0.2–1.0 ng mL^{-1} 2.3 ng mL^{-1}	Total content	[59]
MPB, EPB, PPB, BPB	– Enzymatic hydrolysis with β-glucuronidase – Add acetic acid – SPE (Strata-X)	LC-MS/MS (ESI-)	0.08–0.30 ng mL^{-1}	Total content	[60]
MPB, EPB, PPB, BPB	– Enzymatic hydrolysis with β-glucuronidase – On-line SPE (C18)	LC-MS/MS (ESI-)	0.2–0.7 ng mL^{-1}	Total content	[61]
MPB, EPB, PPB, BPB	– Enzymatic hydrolysis with β-glucuronidase – SPE (C18)	LC-MS/MS (ESI-)	0.46–0.57 ng mL^{-1}	Total content	[62]
TCS, TCC, BP-3 MPB, EPB, PPB, BPB, BzPB	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – Automated SPE (Strata XL)	LC-MS/MS (ESI-)	0.01–0.06 ng mL^{-1} 0.07 ng mL^{-1} 0.07–0.4 ng mL^{-1}	Total content	[63]

Table 2
Analytical methods for the determination of PCPs in plasma, serum and blood.

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
BP-1, BP-2, BP-6, BP-8	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Add acetone and centrifuge – Dilute with NaCl (5%) and adjust pH (2) – DLLME	LC-MS/MS (ESI+)	0.1–0.3 ng mL^{-1}	Total and free forms content	[64]
BP-3	– Mix with ACN and centrifuge	LC-UV	0.01–0.5 μg mL^{-1}	Plasma free forms	[65]
MX	– Mix with formic acid – LLE with n-heptane – Clean-up with a silica gel column	GC-ECD	0.1 ng mL^{-1}	Plasma Free forms	[66]
BP-3	– Adjust pH (7.4) – Mix with ACN and centrifuge	LC-UV	80 ng mL^{-1}	Plasma Free forms	[29]
HHCB, AHTN, ADBI, AHMI, DPMI, ATII	– Mix with ACN – LLE with n-pentane – Clean-up with a silica gel column and an aluminum oxide column	GC–MS (CI-)	0.012–0.062 ng mL^{-1}	Plasma Free forms	[67]
TCS	– Acid hydrolysis with hot H_2SO_4 – LLE with n-hexane/acetone – Clean-up with H_2SO_4 – Derivatize with PFBCl	GC–MS (EI)	LOQs 0.009 ng g^{-1} (plasma) 0.05 ng g^{-1} (serum)	Plasma and serum Total content	[68,70]
HHCB, AHTN, ADBI, MM	– Mix with 0.1 M formic acid and MeOH – SPE (C8 cartridges) – SPME (PDMS/DVB 65 μm fiber)	GC–MS (EI)	0.03–0.3 ng mL^{-1}	Serum Free forms	[69]
BP-3	– Mix with ACN and centrifuge	LC-UV	3.9 ng mL^{-1}	Plasma Free forms	[41]
TCS	– Mix with formic acid and dilute with water – SPE (HLB cartridges) – Clean-up with Florisil cartridges – Derivatize with PFPA	GC–MS (EI)	LOQ 0.09 ng mL^{-1}	Serum free form	[71]
BP-3 MPB, EPB, PPB, BPB, BzPB TCS	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Mix with formic acid and centrifuge – On-line SPE (C18)	LC-MS/MS (APPI-)	0.5 ng mL^{-1} 0.2–0.4 ng mL^{-1} 1.1 ng mL^{-1}	Serum Total content	[72,73]
HHCB, AHTN, ADBI, AHMI, DPMI, ATII, MX, MK, MT, MM, MA	– Mix with ACN – LLE with n-pentane – Clean-up with a silica gel column and an aluminum oxide column	GC–MS (CI-)	0.003–0.062 ng mL^{-1}	Plasma Free forms	[74]
MX, MK, HHCB, AHTN, ADBI, ATII, AHMI	– Mix with methanol – LLE with n-hexane – Clean-up with a glass chromatography column	GC–MS (EI)	0.13–0.15 ng mL^{-1}	Plasma Free forms	[75]
MX, MK, MM, HHCB, AHTN+PBDEs, a HHCB metabolite	– LLE with hexane – Clean-up with GPC with Bio-beads S-X3 – Clean-up with a silica gel packed cartridges	GC–MS (EI)	LOQ 1.0 ng g^{-1}	Maternal and cord serum Free forms	[76]
MPB, EPB, PPB, BPB, BzPB	– Enzymatic hydrolysis with β-glucuronidase – Add formic acid – Automated SPE (Strata XL)	LC-MS/MS (ESI-)	0.02–0.36 ng mL^{-1}	Serum Total content	[50]
TCC + 2 oxidative metabolites	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Mix with formic acid and centrifuge – On-line SPE (C18)	LC-MS/MS (APPI-)	0.1 ng mL^{-1}	Serum Total content	[51]
MPB, EPB, PPB, BPB, BzPB	– Automated SPE (Rapidtrace Automated Workstation) – SPE (Oasis HLB)	UPLC-MS/MS (APCI-)	2.0–7.0 ng mL^{-1}	Plasma Free forms	[77]
TCC + 2 oxidative metabolites	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Dilute with Milli-Q water and centrifuge – On-line SPE (C18)	LC-MS/MS (ESI-)	0.10 ng mL^{-1}	Serum Total content	[52]
TCS + BPA, 4-nNP and 2 phenols	– Mix with ACN and centrifuge – Dilute with deionized water – UAEM-SFO with 2-dodecanol	CE-UV	0.01 ng mL^{-1}	Serum Free form	[53]

Table 2 (*continued*)

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
TCS + 21 substances actives	– Mix with ACN, centrifuge and Filter – Dissolve with water at pH 7 – Continuous SPE (Oasis HLB) – MAD with BSTFA 1% TMCS	GC–MS (EI)	2.9 ng L^{-1}	Blood free form	[54]
TCC	– Acid hydrolysis with HCl – Neutralize with NaOH mixed with acetic acid – LLE with ethyl acetate and centrifuge	ELISA	LOQ 5 ng mL^{-1}	Blood Total content	[55]
MPB, EPB, PPB, BPB	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Add acetone – DLLME	UHPLC-MS/MS (ESI-)	0.1–0.2 ng mL^{-1}	Serum total content	[78]
BP-1, BP-3, BP-8	– Acid hydrolysis with HCl – DLLME	LC-MS/MS (ESI+)	7–8 ng mL^{-1}	Serum total content	[79]

Table 3
Analytical methods for the determination of PCPs in human breast milk, semen, liver, brain, adipose and placental tissue.

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
TCS	– Mix with formic acid – LLE with hexane and clean-up with H_2SO_4 – Derivatize with acetic anhydride	GC–MS (EI)	No data	Milk Free form	[80]
HHCB, AHTN, MK, MX, MM	– Soxhlet extraction – GPC with Bio-beads S-X3 – Clean-up with silica gel packed cartridges	GC–MS (CI)	5 ng g^{-1}	Adipose tissue Free forms	[81]
TCS	– Acid hydrolysis with H_2SO4 – LLE with n-hexane/acetone and clean-up with H_2SO_4 – Derivatize with PFBCl	GC–MS (EI)	LOQ 0.018 ng g^{-1}	Milk Total content	[68]
BP-3 TCC	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Mix with IPA, centrifuge and mix with formic acid – On-line SPE (C18)	LC-MS/MS (APCI-)	0.51 ng mL^{-1} 0.91 ng mL^{-}	Milk Total and free form content	[82]
HHCB, AHTN, ADBI, MM	– Mix with 0.1 M formic acid and MeOH – SPE (C8) – SPME (PDMS/DVB 65 μm fiber)	GC–MS (EI)	0.03–0.3 ng mL^{-1}	Milk Free forms	[69]
MX, MK, HHCB, AHTN	– LLE with hexane – Clean-up with GPC with Bio-beads S-X3 – Clean-up with a silica gel packed cartridges	GC–MS (EI)	2–5 ng g^{-1} lipid	Milk Free forms	[83]
BP-3 TCS MPB, EPB, PPB, BPB, BzPB	– Enzymatic hydrolysis with β-glucuronidase/sulfatase – Mix with MeOH and centrifuge – Dilute with formic acid and on-line SPE (C18)	LC-MS/MS (APCI-)	0.4 ng mL^{-1} 1 ng mL^{-1} 0.1 ng mL^{-1}	Milk Total content	[84]
MX, MK, MM, HHCB, AHTN+PBDEs, a HHCB metabolite	– LLE with hexane – Clean-up with GPC with Bio-beads S-X3 – Clean-up with a silica gel packed cartridges	GC–MS (EI)	LOQ 0.5 ng g^{-1}	Milk Free forms	[76]
BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP	– Homogenize with water – LLE with ethyl acetate and centrifuge	LC-MS/MS (APCI+)	0.07–0.3 ng g^{-1}	Placental tissue Free Forms	[9]
MPB, EPB, PPB, BPB	– Homogenize with water – LLE with ethyl acetate and centrifuge	LC-MS/MS (APCI-)	0.03–0.06 ng g^{-1}	Placental tissue Free forms	[10]
BP-1, BP-3, BP-6, BP-8, 4-OH-BP, MPB, EPB, PPB, BPB + BPA and chlorinated derivatives	– Homogenize with water – LLE with ethyl acetate and centrifuge	LC-MS/MS (APCI-)	0.03–0.2 ng g^{-1}	Placental tissue Free forms	[11]

Table 3 (*continued*)

Analyte	Sample treatment	Analytical technique	LOD/LOQ	Comments	Ref.
MPB, EPB, PPB, BPB	– Centrifuge – Precipitate lipids with ACN and centrifuge – Aqueous phase: – Enzymatic hydrolysis with β-glucuronidase/sulfatase	LC-MS/MS (ESI-)	1 ng mL^{-1}	Milk Total content	[85]
BP-2, BP-3	Lipidic phase: – LLE with n-hexane/acetone and DCM/acetone – Clean-up with GPC	GC–MS	1–2 ng g^{-1} lipid	Free forms	
AHTN, HHCB, ATII, AHMI, ADBI, DPMI+others musks	Lipidic phase: – LLE with n-hexane – Clean-up with silica gel mini column	GC–MS, GC-ECD	2.5–10 ng g^{-1} lipid	Free forms	
BP-1, BP-3, BP-8, THB	– Filter and enzymatic hydrolysis with β-glucuronidase/sulfatase – Add formic acid (pH 3) – SPE (C18)	LC-MS/MS (ESI+)	1–3 ng mL^{-1}	Semen Total content	[48]
MPB, EPB, PPB, BPB, BzPB	– Centrifuge and treat cell-free seminal plasma with β-glucuronidase for enzymatic hydrolysis – Add phosphoric acid – SPE (Strata-XL)	LC-MS/MS (ESI-)	0.03–0.41 ng mL^{-1}	Semen Total content	[50]
TCS	– Ultrasonication with ACN and centrifuge – Derivatize with PFBCl – Clean-up with acidified silica cartridges	GC–MS (EI)	LOQ 0.06 ng g^{-1}	Adipose tissue, brain, liver Free forms except liver (Total and free forms)	[86]
MPB, EPB, PPB	– Add ACN – MIPSPE	LC-UV	LOQs 10–20 ng mL^{-1}	Milk Free forms	[87]

also been studied. However, the number of compounds studied is a small percentage of the total number of PCPs.

3.1. Sample preparation

3.1.1. Sample pretreatment

Urine is the most studied sample. In this biological matrix, the compounds usually appear as free and conjugated forms; therefore an acid or enzymatic hydrolysis step is usually required to determine the total content (free+conjugated). Without the hydrolysis step, it can be obtained the free content, and the difference between free and total contents, would be the conjugated amount. In older studies, it was typical to use acid hydrolysis with concentrated HCl or H_2SO_4 [27,43,55]. Nowadays, the enzymatic hydrolysis by incubation of urine under specific conditions with β-glucuronidase o with β-glucuronidase/sulfatase is the most common technique for sample pretreatment [25,28–35,37–40,42,44–46,48–52,57,59–64]. After enzymatic hydrolysis, the enzyme is usually precipitated with cold acetonitrile, methanol or formic acid, and then, separated by centrifugation. Finally, the supernatant is submitted to the following sample preparation step.

For plasma or serum analysis, blood has to be previously treated to isolate the plasma or serum. Plasma contains a large variety of proteins including albumin, immunoglobulin and clotting proteins such as fibrinogen. It is obtained by centrifugation of fresh blood containing an anticoagulant. In contrast, serum is prepared by centrifugation of blood samples without anticoagulant. Therefore, serum is plasma without clotting proteins. Once the plasma/serum is obtained, if total content of compounds wants to be determined, a hydrolysis step either with acid [68,70,79] or enzymatic treatment [50–52,72,73,78] must be performed. In these matrices, it is very common to precipitate proteins to reduce matrix interferences. This procedure is usually achieved by mixing the sample with organic solvents, such as acetonitrile [29,41,53,54,65,67,74], methanol [75], formic acid [51,71–73] or a mixture of an organic acid and an organic solvent [69]. Proteins are denatured, precipitated and separated by centrifugation.

Regarding the analysis of breast milk or semen, analogously to the cases of urine and blood, for the determination of the total content, an acid [76] or enzymatic hydrolysis [50,82,84,85] must be carried out. It is also usual the addition of acetonitrile [87], formic acid [80], isopropanol [82], methanol [84] or methanol containing formic acid [69] to precipitate proteins. Finally, related to other human samples such as placenta, liver, brain or adipose tissue, a homogenization step is required. Placenta homogenization is done using an ultrasound probe that allows break up tissue, and after it, shaking with deionised water [9–11] whereas liver and adipose tissue homogenization is done simply mixing [86].

3.1.2. Sample treatment

Due the complexity of biological samples, an extraction technique is usually required to purify and isolate the target compounds from the matrix. Moreover, because of PCP levels in human samples are very low, these extraction techniques must be able to concentrate the analytes and therefore to improve the sensitivity of the analytical method. Tables 1–3 summarized the extraction techniques used in the methods published in the literature. Liquid–liquid extraction (LLE) and solid-phase extraction (SPE) have been widely used. In order to reduce the solvent

amounts and to increase concentration factors, microextraction techniques such as solid-phase microextraction (SPME), stir-bar sorptive extraction (SBSE), dispersive liquid–liquid microextraction (DLLME), membrane assisted liquid–liquid extraction (MALLE), ultrasound assisted emulsification microextraction with solidification of floating organic droplet (UAEM-SFO) or hollow-fiber liquid-phase microextraction (HF-LPME) have also been proposed.

3.1.2.1. Liquid–liquid extraction. It is well known that LLE is a time-consuming technique that often requires large volumes of organic solvents and it is difficult to automate. There are some examples in the literature which use LLE for the extraction of BPs from human samples. Thus, some of these compounds has been extracted from urine using LLE with ethyl acetate [34] and LLE with methyltert-butyl ether/ethyl acetate (1:1, v/v) [46,57]. Obtained LOQs using ethyl acetate were up to 3 times lower than those using the mixture methyltert-butyl ether/ethyl acetate (0.28 ng mL^{-1} vs. 1.0 ng mL^{-1} for BP-1). LLE with ethyl acetate was also employed to extract several BPs from placenta tissue samples [9,11], with LODs lower than 0.3 ng g^{-1}.

Regarding antiseptics, TCC and TCS have been extracted from human samples using LLE with solvents covering a wide range of polarity and mixtures of them. For example, LLE with ethyl acetate was used for the determination of TCC in serum [55] and TCS and TCC in urine [34]; with hexane, for the determination of TCS in breast milk [80]; and with hexane/acetone (9:1, v/v), for the determination of TCS in plasma and breast milk [68], being the LOQ in plasma 55 times lower than the one obtained in urine (0.009 ng g^{-1} vs. 0.5 ng g^{-1}).

In relation to musk fragrances, LLE with a non-polar organic solvent, typically hexane, has been one of the most used techniques to extract these compounds from human samples. It was used for the determination of several nitro and polycyclic musks in plasma [75], breast milk [76,83] and maternal and cord serum [76]. The lowest LODs were obtained in plasma (from 0.13 to 0.15 ng mL^{-1}). Other less common extraction solvents such as n-heptane [66] and n-pentane [67,74] were successfully used to extract musk fragrances from plasma samples. The LODs obtained with n-pentane were markedly better than the ones raised when n-heptane was used (up to 33 times, 0.003 ng mL^{-1} vs. 0.1 ng mL^{-1} for MX).

Regarding preservatives, LLE has been scarcely employed. It has been used to extract several parabens from urine with ethyl acetate [34,58]. LOQs were calculated from the value of the lowest acceptable calibration standard [34] or estimated as ten times the signal to noise (*S*/*N*) ratio [58]. Better sensitivity was obtained in the first case (0.02–0.03 ng mL^{-1} vs. 0.2–1 ng mL^{-1}). In addition, LLE with ethyl acetate was also employed to extract parabens from placental tissue samples [10,11] obtaining LODs lower than 0.06 ng g^{-1}.

3.1.2.2. Solid-phase extraction. SPE has been widely used for the analysis of PCPs. It is well adapted to multi-residue analysis, including compounds that display a wide range of polarities and physic-chemical properties. SPE can be used off-line, on continuous, or coupled on-line to a chromatographic technique. Octadecyl silica sorbents (C18) have been widely used for the analysis of BPs in human samples using SPE in the off-line mode. For example, it was used for the determination of four BPs in urine and semen [48]. Elution was carried out with acetone. Obtained LODs were much lower in urine (0.027–0.103 ng mL^{-1}) than in semen (1–3 ng mL^{-1}). Recently, this sorbent has been used for the determination of BP-3 and four parabens in urine samples, using acetonitrile as elution solvent [28]. Good sensitivity was achieved with LODs from 0.09 to 0.3 ng mL^{-1}. C8 silica base sorbent has been also employed to extract BPs from human samples. Thus, it was employed for the determination of BP-3 and BP-1 in urine [27,38] using methanol/trifluoroacetic acid (99:1, v/v) as elution solvent. Achieved LOD for BP-3 was 20 times lower than for BP-1 (2 ng mL^{-1} vs. 40 ng mL^{-1}).

Regarding antiseptics, HLB (divinylbenzene/*N*-vinylpyrrolidone copolymer) has been the favorite SPE sorbent to study these compounds in human samples. Thus, it was employed in the off-line mode to extract TCS in serum [71], and on continuous mode to extract this compound from urine and blood [54]. Elution was carried out with methanol/dichloromethane (1:1, v/v) and ethyl acetate, respectively. Lower LOD were obtained with the method using off-line SPE (0.09 ng mL^{-1} vs. 0.6 and 2.9 ng mL^{-1}).

In the case of musk fragrances, SPE has been scarcely used. Thus, we have only found one study in which SPE with C8 bonded silica sorbent was used to extract these compounds from serum and breast milk samples [70]. However, SPE with silica [67,68,75] and gel permeation chromatography (GPC) in combination with this [77,82,84] have been commonly used to clean-up and purify extracts prior the musk fragrances analysis.

Related to preservatives, SPE has been widely used to extract parabens from human samples. Strata-X (surface-modified styrene-divinylbenzene polymer) has been one of the most used sorbents. Thus, it was employed for the determination of these compounds in urine, [50,60] serum, and semen samples [50]. Elution was carried out with acetonitrile and acetonitrile followed by ethyl acetate, respectively. Both methods achieved similar sensitivity being serum the matrix with the lowest LODs. This procedure was also employed to extract several parabens, TCS and BP-3, among other phenols, from urine samples [63]. C18 sorbent has been also used in the analysis of parabens. For instance, it was employed to extract these compounds from urine samples [35,62] using methanol as elution solvent. Similar sensitivity was achieved with both methods, with LODs lower than 0.57 ng mL^{-1}. HLB polymeric sorbent has also been used for the determination of parabens in human samples. Thus, it was employed to extract five parabens from plasma samples [77]. Methanol was chosen as elution solvent and a moderate sensitivity was achieved with LODs less than 7 ng mL^{-1}.

Recently, molecularly-imprinted polymers (MIPs) have been used to create the so called molecularly-imprinted SPE (MISPE) sorbents. The concept of MISPE is based on the same main four steps as conventional SPE. However, the principle of adsorption is based on a different mechanism, so a different method development strategy is required. Since the advantage of MISPE is the selectivity, it is important to optimize the selective retention of the target analyte(s) to the imprints and to suppress non-selective interactions to the polymer surface. At its highest point of selectivity, the MIP decreases the non-specific interactions and this produces a drastic reduction of the ionic suppression in mass spectrometry. Despite all their advantages regarding selective extraction, there is not much literature about MIPs and PCPs analysis in human samples. We have only found one work that used a MIP-SPE sorbent to extract parabens from breast milk. In this work, 10 mg of the MIP was packed in micro-disc SPE. The elution was carried out with acetonitrile and obtained LOQs ranged from 10 to 20 ng mL^{-1} [87].

Because of its simplicity, on-line SPE coupled to liquid chromatography coupled mass spectrometry (LC-MS/MS) has been widely employed for the determination of PCPs in human samples [30–33,45,49,51,52,59,61,72,73,82,84]. Automated on-line SPE-LC systems are usually composed for an autosampler, two HPLC pumps, and one six-port switching valve. During on-line SPE-LC, the sample is loaded onto a SPE column where the analytes are retained while the unretained matrix components are washed

away. Then, the analytes are sent to the analytical LC column. Because the evaporation and reconstitution steps, usually present in off-line SPE, are eliminated, on-line methods are less labor intensive than off-line. However, the conventional on-line SPE has some limitations [88]. The starting organic content of the LC solvent gradient is limited by the minimum organic content needed to elute the analytes from the SPE column; furthermore, if the initial organic content is too low, LC signals from the analytes that bind strongly to the SPE column will tail. These problems are avoided by using peak focusing, i.e. diluting the SPE eluate before LC through a mixing device. This technique has been successfully applied to analyze PCPs in urine [30–33,45,49,51,52,61], serum [51,52,72,73] and breast milk [82,84].

3.1.2.3. Microextraction techniques. These techniques are based on equilibrium processes. Thus, SPME is based on the partition equilibrium of the analyte between the sample and a sorbent. Its combination with gas chromatography (GC) is particularly suitable for the determination of volatile and semi-volatile non-polar compounds. Although SPME minimizes disadvantages of conventional techniques like solvent consumption or time required, it has been scarcely used for the determination of PCPs in human samples. Their limitations are mainly related to the reduced possibility of method manipulation and the limited choice of selective commercial sorbents. For instance, three SPME fibers (polydimethylsiloxane, PDMS; polyacrilate, PA; and carbowax-divinylbenzene, CW/DVB) and different experimental set-ups (i.e., equilibrium time and maximum desorption temperature and time) were compared to optimize direct SPME of three BPs in urine [26]. The best recoveries were achieved with CW/DVB, and 10–15 min of equilibrium time was considered suitable. On the other hand, four musk compounds were measured in serum and breast milk samples by using a combined approach of SPE with C8 cartridges and SPME with a PDMS/DVB fiber [69]. Obtained LODs for musk fragrances were markedly lower than those obtained for BPs (0.03–0.3 ng mL^{-1} vs. 5–10 ng mL^{-1}).

Stir-bar sorptive extraction (SBSE) is a technique based on the same principles as SPME with the advantage of a much larger polymer coating of PDMS. Thus results in higher sample capacity and extraction efficiencies. The main drawback of SBSE is that commercial PDMS-coated stir bars can be used only to analyze non-polar compounds. Extraction time is considered the most important parameter affecting SBSE. Once the extraction has concluded, analytes must be desorbed. Thermal desorption (TD) is the most used technique, although it is also possible to carry out a liquid desorption (LD). SBSE has been successfully applied for the determination of TCS with both TD [40] and LD [56] in urine samples. The LOQ of the TD-GC–MS method was 100 times lower than the one of the LD-LC-DAD method (0.1 ng mL^{-1} vs. 10 ng mL^{-1}). SBSE with TD was also used for the determination of five BPs in urine samples [42] with LODs lower than 0.1 ng mL^{-1}.

Ionic liquids (IL) have various advantages over traditional organic solvents, such as low vapor pressure, high stability, high viscosity, moderate dissolvability of organic compounds, adjustable miscibility and polarity, good extractability for different organic and inorganic compounds, as well as the possibility of using longer sampling time and larger droplet volume [89]. This novel extraction technique, using the ionic liquid 1-hexyl-3-methylimidazolium hexafluorophosphate, was applied for the determination of BP-3 in urine. Moderate sensitivity was achieved with a LOD of 1.3 ng mL^{-1} [36].

Another microextraction technique is the dispersive liquid–liquid microextraction (DLLME). The extraction of the analytes takes place in a dispersion of an extracting solvent in water. To achieve the dispersion, a second solvent (called dispersing solvent) is used. The process involves the rapid injection of the mixture of extracting and dispersing solvent, to a water sample. Then, a dispersion which facilitates fast extraction of analytes from water samples is formed. The dispersion is removed by centrifugation and the extraction solvent containing the analytes, is taken for analysis with a microsyringe. The main advantages of this technique are simplicity and rapidity. Recently, it has been applied for the determination of several BPs in serum samples by Vela-Soria et al. [78] and Tarazona et al. [79]. Better sensitivity was achieved by Vela-Soria, with LODs up to 70 times lower for BP-8 (0.1 ng mL^{-1} vs. 7 ng mL^{-1}). This author also used DLLME for the determination of parabens in serum [64]. LODs were in the same range than those obtained for BPs. Acetone and trichloromethane were selected as disperser and extraction solvent, in all the mentioned studies.

Hollow-fiber liquid-phase microextraction (HF-LPME) is a technique based on the use of polypropylene porous hollow fibers. The analytes are extracted from aqueous samples, through a thin layer of organic solvent (several microlitres) immobilized within the pores of a hollow fibers, and into an acceptor solution inside the lumen of the fiber. Reproducibility and the obtaining clean extracts are some of its advantages. Kawaguchi et al. [44] applied this technique for the determination of four BPs in urine, using toluene as extraction solvent. A good sensitivity was achieved with LODs from 0.005 to 0.010 ng mL^{-1}.

The ultrasound-assisted emulsification microextraction and solidification of floating organic droplet (UAEM-SFO) combines UAEM (ultrasound assisted emulsification microextraction), based on a micro-volume of water-immiscible extraction solvent being dispersed into the sample under an ultrasound frequency, and SFOME (solidification of floating organic drop microextraction), where a microdrop of extraction solvent with low density and melting point near room temperature, is delivered to the surface of an aqueous sample by agitation with a stirring bar in the bulk of solution. The extraction solvent is solidified at low temperature within the ice bath and collected easily. The combination of both techniques, allows a speed up mass transfer and therefore shorter extraction time. Wang et al. applied this technique for the determination of TCS in urine [53]. They used 2-dodecanol as extraction solvent and the obtained LOD was 0.01 ng mL^{-1}.

3.2. Analytical techniques

Despite performing a complete and exhaustive sample treatment to eliminate potential interfering compounds from the matrix, an appropriate analytical separation technique must to be selected in order to enhance the determination of the target compounds. Tables 1–3 show the most commonly employed analytical techniques for the detection and quantification of PCPs in human samples. GC or LC coupled to MS or MS^2 are more usual choice. Capillary electrophoresis (CE) has been scarcely used maybe because of the high LODs compared with the ones obtained with LC or GC. However, CE-UV has been successfully used for the determination of TCS in urine [53].

The selection of GC or LC is usually based on the physicochemical properties of the analytes. LC is selected to determine more polar and less volatile compounds, while GC is used to quantify volatile or volatizable compounds. Thus, whereas musk fragrances can be easily determined by GC [67,68,70,75–77,82,84], for other PCPs, as desinfectants, it is necessary a derivatization prior to GC analysis [54,68,70,71,80,86]. PCPs have been usually derivatized by using silylating or acylation reagents. For example, TCS has been analyzed in urine and serum samples by GC–MS previous derivatization with bis(trimethylsilyl)-trifluoroacetamide (BSFTA) [54], pentafluropropionic anhydride (PFPA) [71] or pentafluorobenzoyl chloride (PFBCl) [68,86]. The main advantage of pentafluoro reagents compared to silylation reagents is that they

turn the analytes into highly electrophilic derivatives by introducing 5 or 10 fluorine atoms to improve sensitivity and selectivity in MS detection. Microwave assistant derivatization (MAD) is an efficient technique in order to reduce the derivatization times [54]. The detection limits obtained in this method were 0.6 and 2.9 ng L^{-1} for urine and serum samples, respectively.

MS with electron impact (EI) is the most commonly applied technique in GC–MS [26,40,42–44,54,68,69,71,75,76,80,81,86]. Two important advantages of EI ionization are the small influence of molecular structure on response and the large number of characteristic fragment. Chemical ionization (CI) has also been used and as a soft ionization mode, provides information on the fragmentation pattern useful for structure identification. Negative CI with ammonia as reagent gas was used for the determination of nitro and polycyclic musks in plasma [67,74] and adipose tissue samples [81].

Because most PCPs are polar, non-volatile and thermally-labile compounds, the best choice is usually LC. As shown in Tables 1–3, LC has been selected in several studies to determine preservatives, benzophenone UV-filters and antimicrobials with different detectors coupled to the LC. For example, UV–vis detection has been widely used for the determination of BPs in human samples. These compounds exhibit a high absorbance in the UV range of the electromagnetic spectrum. Thus, LC-UV has been employed to determine BP-1, BP-3 and BP-4 in urine [25,27,29,36,38,41,47,65]. However, UV–vis detection has been scarcely used for the determination of other PCPs. Thus, we have only found a work that uses LC-DAD for the determination of TCS in urine samples [56] and another one for the determination of parabens (MPB, EPB and PPB) in breast milk [87]. LC with fluorimetric detection (FLD) has not been very used for the determination of PCPs because the majority of them do not exhibit native fluorescence.

The recent advances in analytical instrumentation have allowed the unequivocal identification and confirmation of the presence of any compound at very low levels using LC-MS^2. The triple quadrupole (QqQ) is the most common, useful and sensitive tool for PCPs analysis [28,30–35,37,39,45,46,48–52,57–64,72,73,77–79,82,84,85]. The MRM allows monitoring two transitions between precursor and product ions; it is possible to quantify and confirm the presence of PCPs in human matrices at very low concentration levels. Schlumpf et al. [85] reported a multi-residue analytical method for the determination of different groups of PCPs in breast milk samples.

Regarding LC-MS interfaces, electrospray ionization (ESI) is the most frequently used ionization mode. It is a soft ionization technique, suitable for polar and moderately non-polar compounds. However, a critical aspect when using ESI for quantitative analysis is the influence of ion suppression or enhancement in complex samples. Atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) have also been used as interface in the LC-MS^2 analysis of PCPs. They provide more ionization options for low polarity substances. Although in less extent than in ESI, matrix effect can also appear. Many authors [28,30–35,37,45,49,50,52,72,73] use appropriate isotopically labeled compounds as surrogate or internal standards (i.e., MPB-d_4, EPB-d_4, PPB-d_4, BPB-d_4, ^{13}C-BP-3, $^{13}C_{12}$-TCS, TCC-d_7, $^{13}C_6$-TCC) as solution in order to compensate matrix effects for the analogous native analytes (MPB, EPB, PPB, BPB, TCS and TCC).

4. Conclusions

An increasing number of studies demonstrate the presence of a large amount of PCPs (preservatives, antimicrobials, benzophenone UV-filters and musk fragrances) in a great variety of human samples, from urine or serum to semen, adipose tissue or placental tissue. In recent years, several analytical methods have been developed to determine these compounds and the extraction techniques tend to minimize steps and to use less solvent.

There is an increasing demand for analytical procedures to extract and to identify a sufficiently broad variety of substances. Multiresidue methods are being developed for the determination of several families of PCPs with one extraction step and limited sample preparation, which is one of the most critical stages of the analytical procedure; in addition to the classic LLE and SPE, microextraction techniques are becoming alternatives in the analysis of human samples.

GC–MS^2 and LC-MS^2 are the most powerful analytical techniques for quantifying and confirming the presence of PCPs in human samples. Although GC–MS and GC–MS^2 are widely used, the methods based on these techniques are typically more tedious and complex due, for example, to the necessity of introduce steps of derivatization for certain compounds. However, LC-MS^2 working with QqQ in MRM mode offers the required sensitivity without the need of these stages. Because of advantages such as reduced analysis time and cost, less experimental variability and less contact with the biological samples, on-line-SPE-LC-MS^2 has become in one the most popular techniques for multiresidue analysis of PCPs in human fluids and tissues.

Acknowledgments

This study was supported by the Regional Government of Andalusia (Projects of Excellence P09-CTS-4470 and P09-CTS-5488). The authors are grateful to “Instituto de Salud Carlos III” for the postdoctoral contract (Sara Borrell Program, Grant No. CD012/00462) granted to I. Jiménez-Díaz.

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