Inhalation bioaccessibility of multi-class organic pollutants associated to atmospheric PM$_{2.5}$: Correlation with PM$_{2.5}$ properties and health risk assessment[☆]

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ABSTRACT

Inhalation exposure to fine particulate matter (PM$_{2.5}$) represents a global concern due to the adverse effects in human health. In the last years, scientific community has been adopted the assessment of the PM$_{2.5}$-bound pollutant fraction that could be released (bioaccessible fraction) in simulated lung fluids (SLFs) to achieve a better understanding of PM risk assessment and toxicological studies. Thus, bioaccessibility of 49 organic pollutants, including 18 polycyclic aromatic hydrocarbons (PAHs), 12 phthalate esters (PAEs), 11 organophosphorus flame retardants (OPFRs), 6 synthetic musk compounds (SMCs) and 2 bisphenols in PM$_{2.5}$ samples was evaluated. The proposed method consists of a physiologically based extraction test (PBET) by using artificial lysosomal fluid (ALF) to obtain bioaccessible fractions, followed by a vortex-assisted liquid-liquid microextraction (VALLME) and a final analysis by programmed temperature vaporization-gas chromatography-tandem mass spectrometry (PTV-GC-MS/MS). The highest inhalation bioaccessibility ratio was found for bisphenol A (BPA) with an average of 83%, followed by OPFRs, PAEs and PAHs (with average bioaccessibilities of 68%, 41% and 34%, respectively). Correlations between PM$_{2.5}$ composition (major ions, trace metals, equivalent black carbon (eBC) and UV-absorbing particulate matter (UVPM)) and bioaccessibility ratios were also assessed. Principal Component Analysis (PCA) suggested that PAHs, PAES and OPFRs bioaccessibility ratios could be positively correlated with PM$_{2.5}$ carbonaceous content. Furthermore, both inverse and positive correlations on PAHs, PAEs and OPFRs bioaccessibilites could be accounted for some major ions and metal (oid)s associated to PM$_{2.5}$, whereas no correlations comprising considered PM$_{2.5}$ major ions and metal (oid)s contents and BPA bioaccessibility was observed. In addition, health risk assessment of target PM$_{2.5}$-associated PAHs via inhalation was assessed in the study area considering both total and bioaccessible concentrations, being averaged human health risks within the safe carcinogenic and non-carcinogenic levels.

Author statement

Joel Sánchez-Piñero: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft.; Natalia Novo-Quiza: Methodology, Investigation.; Cristina Pernas-Castaño: Methodology, Investigation.; Jorge Moreda-Piñeiro: Conceptualization, Formal analysis, Writing – original draft, Supervision.; Soledad Muniategui-Lorenzo: Writing – review & editing, Funding acquisition.; Purificación López-Mahía: Writing – review & editing, Funding acquisition, Project administration.

1. Introduction

According to the World Health Organization (WHO), outdoor air pollution is considered to be responsible of approximately 3 million deaths worldwide every year (WHO, 2016). Among air pollutants, atmospheric particulate matter (PM) constitutes an important part of air pollution that represents an important risk for human health worldwide,

being classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1) (IARC, 2013). Fine particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) is the air pollutant that trigger the most relevant health problems according to the Environmental European Agency (EEA), estimating that 379,000 premature deaths in 2018 were attributed to $PM_{2.5}$ across the 27 EU Member States and the United Kingdom (EEA, 2020). These particles could penetrate deep in the organism after inhalation and their exposure have been associated with several negative outcomes, being pulmonary and renal function decreasing, lung cancer, damage to DNA, and cardiovascular, reproductive and endocrine alterations the most reported (Brook et al., 2010; Anderson et al., 2012; Hoek et al., 2013; Quarato et al., 2017; Burnett et al., 2018; Simonetti et al., 2018; Tobías et al., 2018; Muñoz et al., 2019). Although the mechanisms by which PM exert adverse health effects in human health are still not clear, they are thought to depend on its chemical composition as several toxic substances such as metal (oid)s and organic pollutants are part of it (Galvão et al., 2018). In the present study, organic compounds concerning polycyclic aromatic hydrocarbons (PAHs), phthalate esters (PAEs), organophosphorus flame retardants (OPFRs), synthetic musk compounds (SMCs) and bisphenols were considered because of their toxicity and ubiquity in the environment (Moon et al., 2012; Kim et al., 2013; Wei et al., 2015; Abdel-Shafy and Mansour, 2016; Hou et al., 2016; Usman et al., 2019; Y. Gao et al., 2019; Hlisníková et al., 2021; Sedha et al., 2021), being many of them classified as high-production volume (HPV) chemicals by the United States Environmental Protection Agency (USEPA) (USEPA, 2021).

In the last years, many studies concerning the assessment of the maximum fraction of PM-bound pollutant that can be dissolved in lung fluids (i.e., bioaccessible fraction) have been carried out as being a more realistic methodology to understand the effects of PM in human health, avoiding the overestimation associated to the use of total content concentrations (Kastury et al., 2017; Wei et al., 2018; Ren et al., 2020). According to the literature, physiologically based extraction tests (PBET) using simulated lung fluids (SLFs) are the most applied methodology to estimate PM-bound pollutants inhalation bioaccessibilities because of being fast, simple and low-cost in comparison with *in vivo* and *in vitro* using cultured cells methodologies (Kastury et al., 2017; Clippinger et al., 2018). PBET methodology consists of the use of SLFs for extracting pollutants from PM (i.e., bioaccessible fraction) under controlled conditions (temperature, agitation, solid-liquid ratio (S/L) and extraction time) similar to those found human body. Although there is not a standardized method, the most used conditions are 37 °C, gentle agitation to prevent filters agglomeration, 20 mL of SLF, S/L above 1:500 to avoid SLF saturation and 24 h of extraction time (Kastury et al., 2017; Ren et al., 2020). Since particle size affects lung deposition, an appropriate selection of SLFs according to PM fraction is essential in order to obtain the most biological relevant data in bioaccessibility assessments (Labiris and Dolovich, 2003). Among them, Gamble's solution, simulated epithelial lung fluid (SELF) and artificial lysosomal fluid (ALF) have been the most used as being representative of different lung regions. Gamble's and SELF solutions (pH 7.4) would simulate the fluid lining the lung epithelium in tracheobronchial region, where PM_{10} fraction is more likely to deposit (Kastury et al., 2017; Ren et al., 2020). On contrary, since $PM_{2.5}$ trends to deposit in the deep lung and stimulate particles engulfment by alveolar macrophages, ALF solution (pH 4.5) was considered in the present study because of simulating the acidic environment after phagocytosis (Midander et al., 2007; Ren et al., 2020; Luo et al., 2021). Basing on available literature, *in vitro* inhalation bioaccessibility methods were focused on PM-associated metal (oid)s (Guney et al., 2016; Leclercq et al., 2017; Žero et al., 2017; Hernández-Pellón et al., 2018; Huang et al., 2018; Kastury et al., 2018), while studies concerning organic compounds were recently addressed for PAHs in PM (Li et al., 2019; Zeng et al., 2019, 2021; Guo et al., 2021; Sánchez-Piñero et al., 2021a) and indoor dust (Luo et al., 2021), OPFRs in PM (Zeng et al., 2019) and PAEs in indoor dust (Kademoglou et al.,

2018), while studies were not found in the literature for the remaining families. Thus, the main objective of this research is to assess the *in vitro* inhalation bioaccessibility of 49 organic pollutants in $PM_{2.5}$ samples (comprising 18 PAHs, 12 PAEs, 11 OPFRs, 6 SMCs and 2 bisphenols), for which few or no studies have been published. Furthermore, possible associations between bioaccessibility ratios of each compound family and $PM_{2.5}$ optical descriptors and components will be explored, as well as $PM_{2.5}$-bound PAHs health risk assessment by inhalation.

2. Materials and methods

2.1. $PM_{2.5}$ sample collection and study area

$PM_{2.5}$ samples were collected from an industrial site of Vigo city (located on the Northwest coast of Spain, coordinates: 42°12′37.0″N 8°44′11.4″W) using an automatic high-volume sampler DIGITAL DH-77 (Hegnau, Switzerland) at 30 m^3 h^{-1} for 24 h (00:00–23:59, UTC), from 10th January to November 6, 2017, during weekdays. Circular quartz filters of 15 cm of diameter (Ahlstrom Munksjö MK360, Falun, Sweden) were used to collect all samples, which were preconditioned at 300 °C during 12 h before using. Both sampling and filter treatment were according to the European Norm 12,341 (EN 12341:2015) by the European Committee for Standardization (CEN) (CEN, 2015), keeping them at 20 ± 1 °C and relative humidity of 50 ± 5% for 48 h before and during $PM_{2.5}$ mass determination using a microbalance. Also, filters were wrapped in aluminium foil inside envelopes, put inside sealed plastic bags stored and stored in a freezer (−18 °C) after $PM_{2.5}$ mass determination to avoid volatile compounds losses. A total of 52 p.m.$_{2.5}$ samples (in agreement with the minimum coverage for indicative measurements according to the European Commissions' (EC) Directive 2008/50/EC (EC, 2008) were selected considering all the months of the campaign (1 or 2 samples a week, distributed randomly), whose details are given in Supporting Information (Table S1). Moreover, field blanks (blank filters put inside the sampler without $PM_{2.5}$ collection) were collected along with routine samples. Although no studies in the area have been found in literature, anthropogenic $PM_{2.5}$ sources derived from combustion and industrial activity are mostly expected since sampling site is located on an industrial area, as well as marine aerosol contribution derived from the proximity to the sea.

2.2. Chemicals and reagents

16 PAHs SemiVolatile Calibration Mix #5 2000 μg mL^{-1} solution in methylene chloride, including naphthalene (Naph), acenaphthylene (Acy), acenaphthene (Ace), fluorene (Fl), phenanthrene (Phe), anthracene (Ant), fluoranthene (Ft), pyrene (Pyr), chrysene (Chry), benzo(a) anthracene (BaA), benzo(k)fluoranthene (BkF), benzo(b)fluoranthene (BbF), benzo(a)pyrene (BaP), dibenz (a,h)anthracene (DBahA), indeno (1,2,3-cd)pyrene (IP) and benzo (g,h,i)perylene (BghiP) were purchased from Restek Corporation (Bellefonte, PA, USA). Moreover, individual standards of retene (Ret), benzo(e)pyrene (BeP) and benzo(j)fluoranthene (BjF) 10 μg mL^{-1} in cyclohexane purchased from Dr. Ehrenstorfer (Augsburg, Germany) were also included. Deuterium-labelled standards solutions of anthracene d-10 (Ant-d10), chrysene d-12 (Chry-d12) and dibenzo (a,h)anthracene d-14 (DBahA-d14) 10 μg mL^{-1} in cyclohexane and benzo(e)pyrene d-12 (BeP-d12) 100 μg mL^{-1} in cyclohexane were both purchased from Dr. Ehrenstorfer; and a PAH Surrogate Cocktail 200 μg mL^{-1} in methylene chloride:methanol (1:1) containing acenaphthylene d-8 (Acy-d8), benzo(a)pyrene d-12 (BaP-d12), benzo (g,h,i)perylene d-12 (BghiP-d12), fluoranthene d-10 (Ft-d10), naphthalene d-8 (Naph-d8), phenanthrene d-10 (Phe-d10) and pyrene d-10 (Pyr-d10) was purchased by Cambridge Isotope Laboratories (Andover, MA, USA). Additionally, EPA Phtalate Esters (PAEs) Mix 2000 μg mL^{-1} in hexane, containing butyl benzyl phthalate (BBP), bis(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diethyl phthalate (DEP), dimethyl phthalate (DMP) and di-n-octyl phthalate
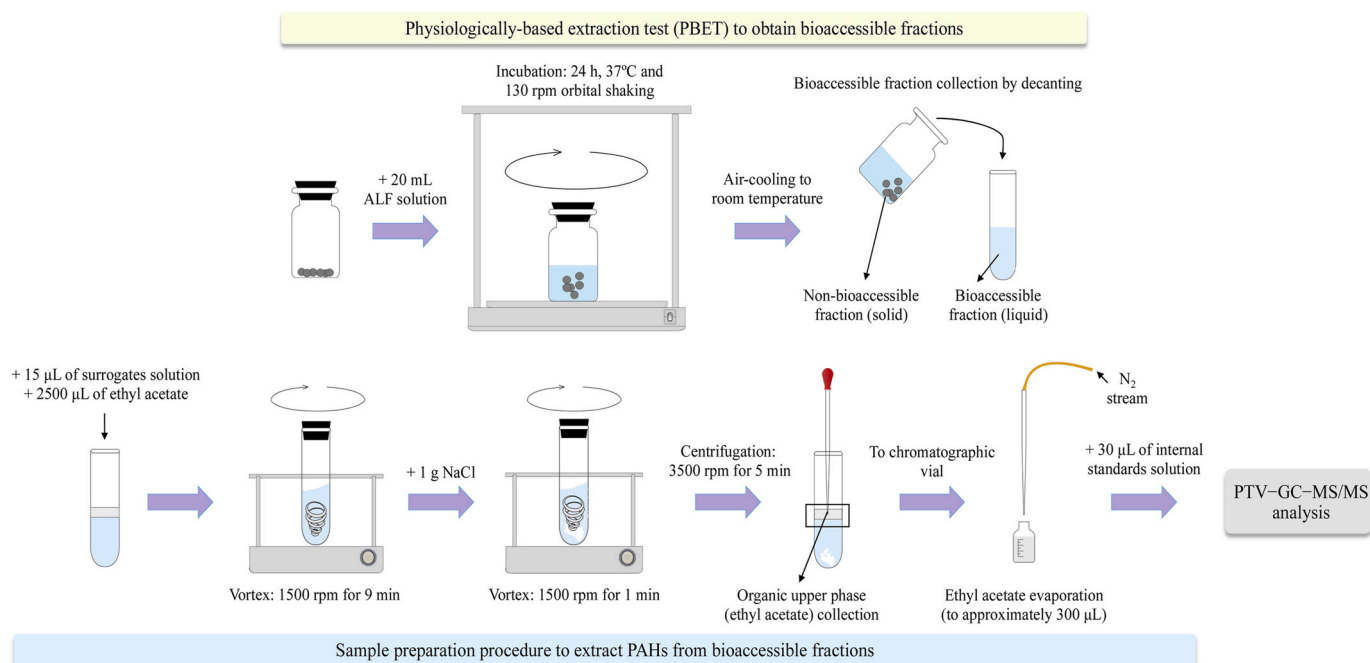
Fig. 1. Scheme of the *in vitro* procedure to obtain organic pollutants bioaccessible fraction from PM$_{2.5}$ samples.

(DOP) was purchased from Sigma-Aldrich (Steinheim, Germany); while a standard solution including bis(2-methoxyethyl) phthalate (DMEP), di-iso-butyl phthalate (DiBP), di-iso-pentyl phthalate (DiPP), di-n-hexyl phthalate (DnHP), dipentyl phthalate (DNPP) and n-pentyl-isopentyl phthalate (NPiPP) 1000 μg mL^{-1} standard solution in acetone was purchased from TechnoSpech (Barcelona, Spain). Benzyl benzoate (BzB) 5000 μg mL^{-1} standard solution in hexane was purchased from Restek Corporation (Bellefonte, PA, USA). Moreover, SMCs standard solution comprising 1-(6-(tert-Butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl) ethenone (Celestolide), 1,3,4,6,7,8-hexahydrocyclopenta[g]is ochromene (Galaxolide), 2-(2-phenyl-imidazo [1,2-a] pyridin-3-yl)-ethylamine (Musk ketone), 1,1,3,3,5-Pentamethyl-4,6-dinitroindane (Musk moskene), 1-tert-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene (Musk xylene) and 6-Acetyl-1,1,2,4,4,7-hexamethyltetralin (Tonalide) 1000 μg mL^{-1} in methanol standard solution; as well as individual deuterium labelled of 1-tert-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene d-15 (Musk xylene-d15) and 6-Acetyl-1,1,2,4,4,7-hexamethyltetralin d-3 (Tonalide-d3) 100 μg mL^{-1} in acetone were acquired from TechnoSpech (Barcelona, Spain). Individual OPFRs standards including tris (1,3-dichloro-2-propyl) phosphate (TDCPP) (95%), tetraethyl ethylene diphosphonate, (TEEdP) (97%), tris(2-ethylhexyl) phosphate (TEHP) (97%), tri-m-cresyl phosphate (TCrP) (95%), tri-n-butyl phosphate (TnBP) (99%), triphenyl phosphate (TPhP) (99%), triphenylphosphine oxide (TPPO) (99%), tripropyl phosphate (TPrP) (99%), tris (2-butox-yethyl) phosphate (TBOEP) (94%), tris (2-chloroethyl) phosphate (TCEP) (97%), tris(chloropropyl) phosphate (TCPP) (99%, mixture of three isomers) were all purchased from Sigma-Aldrich (Steinheim, Germany); while tri-iso-butyl phosphate (TiBP) (95%) was purchased from Carbosynth Ltd (Compton, Berkshire, UK). Triethyl phosphate d-15 (TEP-d15) (99%), tri-n-butyl phosphate d-27 (TnBP-d27) (99%) and triphenyl phosphate d-15 (TPhP-d15) (99%) were all purchased from CDN isotopes (Pont-Claire, Canada). Concerning bisphenols, bisphenol A (BPA) (99%) and bisphenol (BPF) (98%) solid standards were purchased from Sigma-Aldrich (Steinheim, Germany), and bisphenol A d-16 (BPA-d16) 98% was acquired from Dr. Ehrenstorfer. All standard solutions were prepared in ethyl acetate, stored in amber glass vials in a fridge at 4 °C and sonicated for 2 min before using.

As commented before, ALF solution was used as SLF to obtain bio-accessible fractions of PM$_{2.5}$ samples, which was freshly prepared before

analysis using analytical grade reagents and ultrapure water (Milli-Q water purification system, Millipore, Bedford, MA, USA). ALF solution composition is shown in Table S2, being pH adjusted to pH = 4.5–5.0 by using NaOH 50% (w/v) aqueous solution (Midander et al., 2007; Hed-berg et al., 2010; Guney et al., 2017).

2.3. In vitro inhalation bioaccessibility procedure and bioaccessible fraction extraction procedure

A total area of 20.1 cm^2 of each PM$_{2.5}$ samples (PM$_{2.5}$ mass ranging between 0.3 and 4.0 mg) were placed into amber glass bottles and 20 mL of ALF was added. A S/L ratio ranging between 1:5000 to 1:70,000 g mL^{-1} was used, which not exceed the S/L of 1:500 in which SLF saturation could be reached (Caboche et al., 2011; Kastury et al., 2017). Samples were incubated at 37 °C and 130 rpm orbital shaking (to avoid filters agglomeration and ensure a full contact between filters and SLF) during 24 h, using a Rotabit orbital-rocking platform shaker coupled to a Boxcult incubator (J.P. Selecta, Barcelona, Spain) (Fig. 1). Experimental conditions were selected basing on available literature as the absence of a standard methodology concerning *in vitro* inhalation bioaccessibility tests, being performed once per sample.

Once incubation finished, bottles were air-cooled to room temperature and liquid phases (bioaccessible fractions) were separated from filters (non-bioaccessible fraction) by decanting (cleaning bottles with ultrapure water). Afterwards, target compounds were extracted and pre-concentrated by a vortex-assisted liquid-liquid microextraction (VALLME). Bioaccessible fractions of each sample were introduced into glass centrifuge tubes and spiked with 15 μL of surrogates mix in ethyl acetate, containing TEP-d15, Naph-d8, Acy-d8, TnBP-d27, BzB, Phe-d10, Musk xylene-d15, Tonalide-d3, Ft-d10, Pyr-d10, TPhP-d15, Chry-d12, BeP-d12, BaP-d12 and BghiP-d12 (1 μg mL^{-1}) and BPA-d16 (10 μg mL^{-1}). The mixtures were vortexed (1400 rpm) on agitator (VXR basic Vibrax IKA, Staufen, Germany) for 1 min to get homogenized. Then, 2.5 mL of ethyl acetate (LiChrosolv®, Merck-Millipore, Darmstadt, Germany) were added and vortexed again for 9 min to form a cloudy solution. After addition of 1 g of NaCl (Merck-Millipore (Darmstadt, Germany) and vortexing for 1 min (Noche et al., 2011), the mixtures were centrifuged for 5 min at 3500 rpm (Eppendorf 5804, Madrid, Spain) and the upper organic fractions were collected using glass

pipettes (long capillary tips). Finally, the extracts were evaporated by gentle N_2 stream until approximately 300 μL, and 30 μL of internal standards solution (containing Ant-d10 and DBahA-d14, 1 μg mL^{-1}) were added. All extracts were stored in a fridge at 4 °C until further analysis by programmed temperature vaporization (PTV) injector combined with gas chromatography-tandem mass spectrometry (GC–MS/MS). A scheme of the whole procedure to obtain organic pollutants' bioaccessible fractions from PM$_{2.5}$ samples is shown in Fig. 1.

2.4. Quantification by PTV-GC-MS/MS and quality control

Quantification of target compounds was performed by using Thermo Finnigan (Waltham, MA, USA) Trace GC chromatograph equipped with Triplus autosampler, PTV injector, triple quadrupole mass spectrometer (TSQ Quantum XLS) and a DB-XLB column (60 m × 0.25 mm, 0.25 μm film thickness) (J&W Scientific, Folsom, CA, USA). Conditions of PTV and GC oven program were based on the work conducted by Sánchez-Piñero et al. (2021b), together with MS-MS operating in SRM (selected reaction monitoring) mode. Information regarding m/z quantification (Q) and confirmation (C) transitions used for compounds' quantitation are detailed in Tables S3 and S4, which were based on those previously optimised in Sánchez-Piñero et al. (2021b). Transfer line and ion source temperatures were set on 300 °C and 250 °C, respectively; and Xcalibur 2.1 (Thermo Finnigan, Waltham, MA, USA) was used as processor data.

Furthermore, matrix-matched calibration (standards prepared over the residue obtained after extracting blank filters following the procedure described in section 2.3), together with deuterium-labelled surrogate standards, were used to quantitate target compounds basing on relative response factors (RRFs) with respect the surrogates specified in Table S3. Also, surrogate compounds' RRFs were calculated with respect to internal standards (Table S4) to evaluate surrogates compound recoveries in order to monitor the analytical procedure, considering acceptable recoveries within the range of 50–120% according to EN 15549:2008 (CEN, 2008). To control possible contamination during the analysis, at least one field blank and one procedural blank (with not sampled filters) were included in each set of samples. Moreover, the average of field blanks was subtracted from sample values because being representative of samples manipulation during all the procedure (including sampling and analysis).

Average RRFs for each compound were obtained by using at least 7 calibration points, showing satisfactory relative standard deviations (RSDs) < 20% (USEPA, 2018). Moreover, the methodology for analysing target pollutants in bioaccessible fractions were successfully validated in terms of limits of quantification (LOQs), trueness and inter-day precision, as detailed in Supporting Information. A single test was performed for each sample due to the limited sample amount. Thus, PBET inter-day precision to obtain bioaccessible samples (incubation) were tested (RSDs <20% for all quantified compounds) and expanded uncertainties (U$_{exp}$) comprising the whole bioaccessibility methodology procedure (both PBET and VALLME-PTV-GC-MS/MS analysis) were estimated for target compounds (Table S5). Inhalation bioaccessibility ratios (B$_{acc}$), expressed as percentage, were calculated for each compound using the following equation:

$$B_{acc}(\%) = \frac{C_{bioaccessible\ fraction}}{C_{total\ content}} \times 100 \qquad (1)$$

where C$_{bioaccessible\ fraction}$ and C$_{total\ content}$ are bioaccessible concentration (pg m^{-3}) and total concentration (pg m^{-3}), respectively, obtained for each compound and sample.

2.5. Total content pollutants in PM$_{2.5}$ and optical properties

Total content of organic compounds comprising PAHs, PAEs, OPFRs, SMCs and bisphenols in PM$_{2.5}$ samples was assessed following the same

methodology described in Sánchez-Piñero et al. (2021b), while metal (oid)s were analysed by inductively coupled plasma mass spectrometry (ICP-MS) after acid extraction of PM$_{2.5}$ filters (Piñeiro-Iglesias et al., 2003; Moreda-Piñeiro et al., 2015) and major ions were measured by zone capillary electrophoresis (ZCE) after ultrasonic assisted aqueous extraction (Blanco-Heras et al., 2007). Equivalent black carbon (eBC) and UV-absorbing particulate matter (UVPM) were measured by using a Magee SootScan™ OT-21 (Berkeley, CA, USA) transmissometer at 880 nm (interpreted as a measure of light-absorbing carbon analogous to black carbon present on the filter) and 370 nm (designated as an indicator of aromatic organic compounds), respectively (Petzold et al., 2013; Davy et al., 2017; Greilinger et al., 2019; Sánchez-Piñero et al., 2021c). Statistical summary of total organic compounds; eBC, UVPM and major ions; and metal (oid)s concentrations in studied PM$_{2.5}$ samples are shown in Table 1, S6 and S7, respectively.

2.6. Health risk assessment via inhalation

The USEPA's last update to assess health risk assessment by inhalation recommends the use of the calculation of exposure concentrations (ECs) as well as a separately evaluation of carcinogenic and non-carcinogenic risks (USEPA, 2009). However, application of this approach is limited due to only few pollutants could be considered because of the lack toxicological data (inhalation unit risk (IUR) and reference concentration for chronic inhalation exposure (RfC) values) as previously reported (Sánchez-Piñero et al., 2021a). Consequently, inhalation health risk assessment was only conducted for PAHs since there were not found toxicological data to perform an inhalation health risk assessment for the remaining compounds. In this framework, non-carcinogenic risk assessment was conducted for the few PAHs for which toxicological data is available (i.e., BeP and BaP) according to the USEPA's inhalation dosimetry model, whereas BaP-equivalent carcinogenic (BaP$_{Teq}$) concentrations (USEPA, 1993) were combined with the model for carcinogenic risk assessment as allowing the inclusion of all the studied PAHs as well as considering additive toxic effects between PAHs (Nisbet and LaGoy, 1992; USEPA, 1993), using both bioaccessible and total concentrations to assess risk overestimation. Then, BaP$_{Teq}$ concentrations (ng m^{-3}) were calculated in PM$_{2.5}$ samples based on total ([BaP$_{Teq}$]$_{Total}$) and bioaccessible ([BaP$_{Teq}$]$_{Bacc}$) PAHs concentrations, using the following formula:

$$[BaP_{Teq}]_{Total\ or\ Bacc} = \sum (C_i \ x \ TEF_i) \qquad (2)$$

where C$_i$ represents the total/bioaccessible concentration of each PAH in PM$_{2.5}$ samples (ng m^{-3}), and TEF$_i$ is the toxic equivalence factor of the that PAH$_i$ relative to BaP. TEFs used in this study are summarized in Table S8 (Nisbet and LaGoy, 1992; OEHHA, 2005; Samburova et al., 2017).

Moreover, three exposure scenarios concerning (I) residents in the studied area (including children and adults); (II) residents working outside the studied area and (III) workers not living in the area were considered. Then, ECs (μg m^{-3}) considering total and bioaccessible BaP$_{Teq}$ concentrations (EC (BaP$_{Teq}$)$_{Total}$ and EC (BaP$_{Teq}$)$_{Bacc}$, respectively) were calculated for each scenario using equation (3) for carcinogenic risk assessment, while ECs (mg m^{-3}) basing on total and bioaccessible concentrations (EC$_{Total}$ and EC$_{Bacc}$, respectively) for non-carcinogenic risk assessment were calculated following equation (4):

$$EC\ (BaP_{Teq})_{Total\ or\ Bacc} = \frac{[BaP_{Teq}]_{Total\ or\ Bacc} \times ET \times EF \times ED}{AT_c} \qquad (3)$$

$$EC_{Total\ or\ Bacc} = \frac{C_i \times ET \times EF \times ED}{AT_{nc}} \qquad (4)$$

where [BaP$_{Teq}$]$_{Total}$ and [BaP$_{Teq}$]$_{Bacc}$ are BaP$_{Teq}$ total and inhalation bioaccessibility concentrations estimated for each PM$_{2.5}$ sample (μg m^{-3}); C$_i$ represents the total/bioaccessible concentration of each PAH in PM$_{2.5}$

Table 1
Mean, maximum (Max), minimum (Min) (pg m^{-3}) and relative standard deviation (RSD) of pollutants' bioaccessible and total concentrations found in PM$_{2.5}$ samples.

Compound	Bioaccessible concentrations				Total content			
	Mean	Max	Min	RSD	Mean	Max	Min	RSD
PAHs								
Phe	16.2	54.9	<10.7	86	39.7	154	<27.9	96
Ft	21.1	95.8	<4.5	105	54.5	232	<19.8	106
Pyr	20.6	98.5	<4.5	132	107	395	<33.8	100
Ret	35.4	102	<55.3	53	41.5	261	<38.2	106
BaA	28.2	242	<4.6	178	121	1070	<2.9	180
Chry	42.8	238	3.7	118	164	1270	11.3	154
BbF + BjF	142	1060	<5.6	160	546	4440	16.9	164
BkF	35.5	253	<3.0	148	168	1340	8.2	165
BeP	75.3	481	<7.8	146	214	1250	14.7	121
BaP	45.4	403	<2.8	152	171	1420	<2.0	165
DBahA	14.0	96.6	<4.8	153	63.5	463	<7.5	153
IP	69.7	470	<6.0	148	330	2540	9.0	161
BghiP	104	645	5.4	139	413	2710	22.7	141
PAEs								
DNPP	2.6	8.9	<3.6	65	<6.7	9.0	<6.7	23
DnHP	3.0	12.7	<4.4	67	6.2	29.9	<5.5	116
DEHP	184	3380	<146	252	<694	16,100	<694	288
DOP	6.3	54.2	<3.5	137	21.2	130	<4.6	129
OPFRs								
TiBP	198	1010	<25.2	157	340	2050	<38.0	149
TCPP	241	2610	<27.4	191	411	3000	<81.8	127
TPPO	119	1970	<23.0	266	367	2390	<98.4	138
Bisphenols								
BPA	3730	28,000	<375	171	4480	39,800	<304	177

samples (mg m^{-3}); ET is the exposure time (h day^{-1}); EF is the exposure frequency (days year^{-1}); ED is the exposure duration (years); and AT$_c$ and AT$_{nc}$ are the averaging time for carcinogenic risk assessment (70 × 365 × 24 h) and for non-carcinogenic risk assessment (ED × 365 × 24 h), respectively. Values used for each exposure scenario are shown in Table S9.

Consecutively, carcinogenic hazard index (HI$_c$) using total (EC (BaP$_{Teq}$)$_{Total}$) and bioaccessible (EC (BaP$_{Teq}$)$_{Bacc}$) PAHs concentrations were estimated by using equation (5); whilst for non-carcinogenic risk assessment, hazard quotient (HQ$_i$, calculated for BeP and BaP) and subsequent non-carcinogenic hazard index (HI$_{nc}$) were calculated using equations (6) and (7) respectively, using both total (HQ$_{i-Total}$ and HI$_{nc-Total}$) and bioaccessible (HQ$_{i-Bacc}$ and HI$_{nc-Bacc}$) concentrations (USEPA, 2009):

$$HI_c(BaP_{Teq})_{Total\ or\ Bacc} = EC\ (BaP_{Teq})_{Total\ or\ Bacc} \times IUR_{BaP} \quad (5)$$

$$HQ_{i,\ Total\ or\ Bacc} = \frac{EC_{Total\ or\ Bacc}}{RfC_i} \quad (6)$$

$$HI_{nc-Total\ or\ Bacc} = \sum HQ_{i,\ Total\ or\ Bacc} \quad (7)$$

where IUR$_{BaP}$ (because of using BaP$_{Teq}$ concentrations) corresponds with 6.0×10^{-4} (µg m^{-3})$^{-1}$ (USEPA, 2022); and RfC$_i$ for both BeP and BaP is 2.0×10^{-6} (mg m^{-3}) (USEPA, 2022).

2.7. Statistical treatment of data

Statgraphics version 7.0 routine (Statgraphics Graphics Corporation, ST. SC., USA) was used to perform statistical data treatment at 95% confidence level, comprising Shapiro-Wilk and Bartlett's tests (to check normality and homoscedasticity of data, respectively); Pearson's and Spearman's correlations (for linear and non-linear data distributions, respectively); as well as principal component analysis (PCA) and multiple linear regression models in order to explore possible associations between bioaccessibility ratios and PM$_{2.5}$ properties and components (comprising eBC, UVPM and other components such as major ions and

total metal (oid)s content). To facilitate PCA interpretation, bioaccessibility sum ratios (B$_{accSum}$) of each sample were calculated for PAHs (B$_{accSum}$PAHs), PAEs (B$_{accSum}$PAEs) and OPFRs (B$_{accSum}$OPFRs) using the equation as follows:

$$B_{accSum}Compound\ family\ (\%) = \frac{\sum C_{compound\ family-bioaccessible\ fraction}}{\sum C_{compound\ family-total\ content}} \times 100 \quad (8)$$

where $\sum C_{compound\ family-bioaccessible\ fraction}$ and $\sum C_{compound\ family-total\ content}$ are the summation of bioaccessible concentrations (pg m^{-3}) and the sum of total concentrations (pg m^{-3}), respectively, obtained for each sample and compounds belonging to the same family. Compounds enclosed in summations were the same considered for bioaccessibility ratios estimation in the previous section. After half-range and central value transformation (for dataset homogenisation), PCA analysis was carried out by employing the orthogonal transformation method with Varimax rotation and retention of principal components with eigenvalues higher than 1.0. R-Squared and Durbin-Watson statistic tests were used to multivariate analysis based on multiple linear regression model.

Also, LOQ/2 criterion was applied to estimate concentrations < LOQ for mean calculations and health risk assessment. However, concentrations < LOQ were not considered in PCA and bioaccessibility ratios calculations.

3. Results and discussion

3.1. In vitro bioaccessible concentrations and bioaccessibility ratios

Bioaccessible concentrations found in PM$_{2.5}$ analysed samples, together with total concentrations, are summarized in Table 1, showing the mean, maximum, minimum, and RSD values. Concerning all compound families included in the present study, a bioaccessible concentration order of BPA (3730 pg m^{-3}) > PAHs (650 pg m^{-3}) > OPFRs (558 pg m^{-3}) > PAEs (196 pg m^{-3}) was obtained considering the summation of the averages obtained for each family. Attending to the results shown in Table 1, BPA was the only bisphenol that was found in bioaccessible
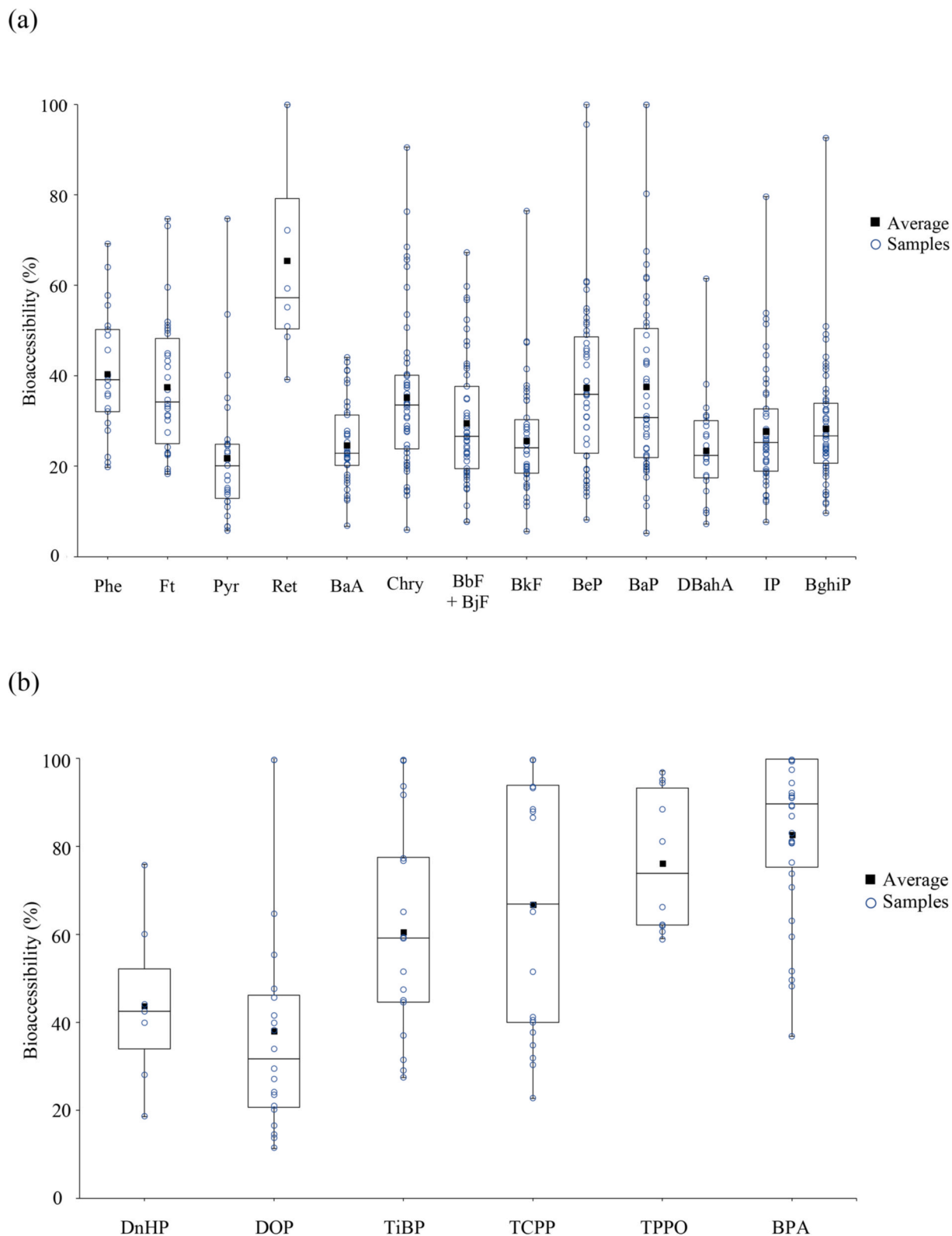
(a)

(b)

Fig. 2. Inhalation bioaccessibility of (a) PAHs and (b) PAEs, OPFRs and BPA obtained for $PM_{2.5}$ samples, expressed as percentage (%).

fractions comprising all studied samples, representing the highest concentration with respect to the other families. However, BPF was found to be <LOQ (314 pg m^{-3}) for all studied samples. Furthermore, PAHs were the most detected compounds among the studied ones, following the bioaccessible average concentration order BbF + BjF (142 pg m^{-3}) > BghiP (104 pg m^{-3}) > BeP (75.3 pg m^{-3}) > IP (69.7 pg m^{-3}) > BaP

(45.4 pg m^{-3}) > Chry (42.8 pg m^{-3}) > BkF (35.5 pg m^{-3}) > Ret (35.4 pg m^{-3}) > BaA (28.2 pg m^{-3}) > Ft (21.1 pg m^{-3}) > Pyr (20.6 pg m^{-3}) > Phe (16.2 pg m^{-3}) > DBahA (14.0 pg m^{-3}). Nevertheless, Naph, Acy, Ace, Fl and Ant were found to be <LOQ in most samples (less than 6% of the samples). Concerning OPFRs and PAEs, bioaccessible average concentrations obtained followed the order TCPP (241 pg m^{-3}) > TiBP (198 pg

m^{-3}) > TPPO (119 pg m^{-3}); and DEHP (184 pg m^{-3}) > DOP (6.3 pg m^{-3}) > DnHP (3.0 pg m^{-3}) > DNPP (2.6 pg m^{-3}), respectively. The remaining PAEs and OPFRs compounds were not included because of being detected in less than 8% of the samples. Furthermore, SMCs were not detected in bioaccessible fractions obtained among all studied samples. Detailed information of concentrations found in bioaccessible fractions for each compound and sample are given in Tables S10 and S11.

Regarding to the current legislation in PM, BaP is the only studied compound with an annual limit of 1 ng m^{-3} (total content in PM$_{10}$) according to European Directive (2004)/107/EC (EC, 2004). No exceedances of the annual value were observed in none of the samples, with a mean bioaccessible BaP concentration of 45.4 pg m^{-3} and a daily maximum value of 403 pg m^{-3}.

The box-whisker plots (Fig. 2) show the wide variation of B$_{acc}$ values among the analysed samples that might be attributed to the heterogeneity of PM$_{2.5}$ samples (corresponding to different PM sources) as suggested in previous studies (Li et al., 2019; P. Gao et al., 2019b). Comprising PAHs (Fig. 2a), average values obtained followed the order Ret (66%) > Phe (41%) > BaP, Ft, BeP (38%) > Chry (36%) > BbF + BjF (30%) > BghiP (29%) > IP (28%) > BkF (26%) > BaA (25%) > DBahA (24%) > Pyr (22%). Averaged B$_{acc}$ values obtained in this study are higher than those reported for PAHs in PM$_{10}$ using Gamble's solution (pH = 7.4) (Sánchez-Piñero et al., 2021a) and PM$_{2.5}$ using SELF (pH = 7.4) (simulated epithelial lung fluid, similar to Gamble's solution combined with lung surfactant 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)) (Li et al., 2019), that might be attributed to the low pH of ALF (pH = 4.5–5.0) as obtained for PAHs-bound PM$_{2.5}$ indoor dust (Luo et al., 2021) and atmospheric PM$_{2.5}$ (Zeng et al., 2019). Low pHs could decrease PAHs adsorption in particles, promoting therefore their release into SLF as suggested by P. Gao et al. (P. Gao et al., 2019a). The acidic environment triggered by macrophages stimulation in lung alveoli was also reported to increase metal (oid)s bioaccessibilities, yet PAHs bioaccessibilities were found to be lower as generally reported for metal (oid)s (Kastury et al., 2017; Ren et al., 2020). Also, results obtained were comparable to the study conducted by Zeng et al. (2021) concerning atmospheric PM$_{2.5}$ samples using SELF, with mean B$_{acc}$ values ranging between 20 and 40%. This suggests that, not only pH but also the additive use of surfactants, could increase PAHs bioaccessibility as also reported for metal (oid)s (Kastury et al., 2017), that would require further study (Ren et al., 2020). Moreover, average B$_{acc}$ values obtained in the present study are similar to those published by Luo et al. (2021) for Chry, DBahA, IP and BghiP in indoor PM$_{2.5}$. However, values obtained for Phe, Ft, Pyr and BaA in this work were around 10% lower than published by Luo et al. (2021), while BaP bioaccessibility was found to be approximately 10% higher. Moreover, PAHs bioccessibilities reported by Zeng et al. (2019) for atmospheric PM$_{2.5}$ are below 5% and 10% (Phe) after 1-day and 15-days simulations respectively, that are much lower than values obtained in our study. Considering average of bioaccessibilities (without including Ret, in order to make more comparable results), an average value of 31% was obtained, that was higher than 17% published by Guo et al. (2021) for atmospheric PM$_{2.5}$ samples. Although some authors studied the influence of PM granulometry on PAHs bioaccessibility, bioaccessibility variability observed was essentially attributed to particle properties linked to PM adsorption/desorption capacity (elemental and organic carbon content, and surface area) and SLFs' properties (pH and components) rather than particle's sizes (Xie et al., 2018; Besis et al., 2022). According to this, it could be a consequence of the presence of citric acid in ALF solution composition (20.9 g L^{-1} in ALF solution, while is not a component of Gamble's solution and SELF formula), which can disrupt the linkages between BC surfaces and hydrophobic organic pollutants (such as PAHs) (Sun et al., 2016). Also, this fact might be a consequence of the ALF's more acid pH in contrast to Gamble's solution, as reported by P. Gao (P. Gao et al., 2019a). Moreover, although the highest bioaccessibility values were observed for some 3–4 condensed rings PAHs (Ret, Phe, Ft and Chry),

Table 2
Factor loadings for (a) PAHs, (b) PAEs, (c) OPFRs and (d) BPA bioaccessibility ratios after a normalized Varimax rotation for the three first principal components (PCs). In bold are highlighted the main contributors to each PC.

(a)	Factor loadings		
	PC1	PC2	PC3
B$_{accSum}$PAHs	0.053	**0.159**	**−0.188**
UVPM	**0.486**	0.150	**−0.224**
eBC	**0.452**	0.066	**−0.195**
Cl$^-$	0.179	**0.205**	0.311
NO$_3^-$	0.244	**0.387**	0.101
SO$_4^{2-}$	**0.369**	**−0.299**	0.080
C$_2$O$_4^{2-}$	**0.426**	−0.109	0.176
NH$_4^+$	0.235	**−0.489**	0.057
K$^+$	**0.390**	−0.033	−0.040
Na$^+$	0.181	**0.190**	0.305
Ca^{2+}	0.168	0.069	−0.175
Mg^{2+}	0.005	0.082	0.057
Fe	−0.080	−0.130	0.045
Pb	0.167	−0.087	0.015

(b)	Factor loadings		
	PC1	PC2	PC3
B$_{accSum}$PAES	**0.260**	**−0.398**	−0.172
UVPM	**0.502**	0.053	0.130
eBC	**0.514**	−0.026	0.035
Cl$^-$	0.161	**0.452**	−0.038
NO$_3^-$	0.209	**0.373**	0.150
SO$_4^{2-}$	**0.433**	−0.071	−0.074
C$_2$O$_4^{2-}$	**0.470**	0.097	−0.231
NH$_4^+$	**0.310**	−0.208	0.013
K$^+$	**0.459**	−0.027	−0.076
Na$^+$	0.167	**0.420**	0.010
Ca^{2+}	0.164	−0.083	**0.474**
Mg^{2+}	−0.003	0.078	0.057
Sb	−0.155	0.354	−0.185

(c)	Factor loadings		
	PC1	PC2	PC3
B$_{accSum}$OPFRs	**0.542**	−0.190	**0.441**
UVPM	**0.436**	−0.037	−0.164
eBC	**0.324**	−0.027	−0.186
Cl$^-$	0.008	−0.015	0.018
NO$_3^-$	0.227	−0.172	**−0.224**
SO$_4^{2-}$	0.209	**0.366**	−0.011
C$_2$O$_4^{2-}$	0.075	0.196	0.061
NH$_4^+$	0.168	**0.582**	0.030
K$^+$	0.208	0.017	−0.076
Na$^+$	0.034	−0.001	0.017
Ca^{2+}	**0.383**	−0.068	−0.128
Mg^{2+}	−0.004	−0.042	−0.043

(d)	Factor loadings		
	PC1	PC2	PC3
B$_{acc}$BPA	0.028	−0.010	−0.106
UVPM	**0.502**	0.058	**−0.365**
eBC	**0.490**	−0.009	**−0.302**
Cl$^-$	0.191	**0.432**	0.204
NO$_3^-$	0.207	**0.452**	−0.081
SO$_4^{2-}$	**0.496**	−0.192	0.181
C$_2$O$_4^{2-}$	**0.509**	−0.032	**0.244**
NH$_4^+$	0.376	**−0.378**	0.250
K$^+$	**0.471**	−0.043	−0.037
Na$^+$	0.174	**0.411**	0.238
Ca^{2+}	0.155	0.029	−0.117
Mg^{2+}	−0.025	0.112	0.061

Pyr was the PAH that show the lowest value of 22% (4 condensed rings); while 5–6 condensed rings PAHs (BbF + BbF, BkF, BeP, BaP, DBahA, IP and BghiP) represented a wide range of bioaccessibilities. Furthermore, relationship between PAHs bioaccessibility ratios and octanol-water partition coefficients (logK$_{ow}$, detailed in Table S12) were not found after Spearman's correlation test (p-values >0.05), unlike as observed for PAHs associated to PM$_{2.5}$ and PM$_{10}$ samples using Gamble's solution

and SELF (Li et al., 2019; Sánchez-Piñero et al., 2021a; Besis et al., 2022).

As it can be seen in Fig. 2b, BPA was observed to be the compound that offered the highest value among all the studied compounds, with an average B_{acc} value of BPA 83%. To the best of our knowledge, there was not found any study concerning inhalation bioaccessibility of BPA, however a high oral BPA bioaccessibility in canned food (92%) were reported by Cunha et al. (2017), that might indicate the great potential of BPA to dissolve in simulated body fluids. Moreover, OPFRs bio-accessibilities followed the order TPPO (77%) > TCPP (67%) > TiBP (61%); while PAEs followed the order DnHP (44%) > DOP (38%) (Fig. 2b). As commented before, scarce data comprising these compounds were found in literature, but average inhalation bioaccessibility for TCPP in the present study was lower than published by Zeng et al. (2019) in atmospheric $PM_{2.5}$, reporting a bioaccessibility value of almost 100%. Furthermore, inhalation bioaccessibilities for TCEP and DOP obtained in this study are higher than oral bioaccessibilities (average values of 47% and 6%, respectively) reported in indoor settled dust (Raffy et al., 2018). Lower oral bioaccessibilities with respect to inhalation ratios might be attributed to the presence of enzymes during the PBET oral procedure. Concerning the remaining compounds, bioaccessibility ratios calculation were not performed because of being bioaccessible and total concentrations < LOQ for all or most of samples. Moreover, an inverse correlation between bioaccessibilities and $logK_{ow}$ (Table S12) were found for BPA, OPFRs and PAEs (Spearman's coefficient of −0.829, p-value <0.05) in studied samples, which would suggest a greater influence of their hydrophobicity in comparison to PAHs. Finally, the differences found in bioaccessibility ratios with respect to available literature evidences the importance of using SLFs in order to obtain biological relevant data and achieve a better understanding of PM-bound pollutants release in the organism (Marques et al., 2011; Calas et al., 2017; Ren et al., 2020).

3.2. Correlations between bioaccessibility ratios and $PM_{2.5}$ properties

As mentioned before, the study of the relationship between inhalation bioaccessibilities obtained in the present study and $PM_{2.5}$ properties comprising eBC, UVPM and other components such as major ions and total metal (oid)s content, was assessed through a statistical study based on PCA and multiple linear regression model. Thus, PCA has been attempted separately for each compound family and BPA, with a data set in which, all quantitated major ions (Cl^-, NO_3^-, SO_4^{2-}, $C_2O_4^{2-}$, NH_4^+, K^+, Na^+, Ca^{2+}, Mg^{2+}), eBC, UVPM, some metal (oid)s concentrations (selected on the basis of their traceability for natural and/or anthropogenic PM sources) and B_{accSum} or $B_{acc}BPA$ (as being the only bisphenol whose bioaccessibility ratio could be calculated) values were the discriminating variables, while the objects were the 52 p.m.$_{2.5}$ samples analysed.

3.2.1. Principal component analysis for PAHs

In Table 2a are shown the main PCs and factor loadings for B_{accSum}PAHs and $PM_{2.5}$ properties, explaining 76% of the total variance by 3 principal components (PCs) which show eigenvalues higher than 1.0. UVPM, eBC, SO_4^{2-}, $C_2O_4^{2-}$ and K^+ are the main contributors to PC1, explaining 40% of total variance; while B_{accSum}PAHs, Cl^-, NO_3^-, SO_4^{2-}, NH_4^+ and Na^+ are the main features in PC2, explaining 22% of the total variance. Finally, in PC3, B_{accSum}PAHs, UVPM, eBC, Cl^- and Na^+ are the main contributors, accounting for 14% of the total variance.

Attending to the results shown in Table 2a, B_{accSum}PAHs are divided between PC2 and PC3. However, PCs explain little information of B_{accSum}PAHs since small coefficients were obtained, accounting for 0.159 and −0.188 in PC2 and PC3, respectively. This would suggest that correlations between B_{accSum}PAHs and PCs, and thus, the main variables that contribute to them, are weak. Considering this limitation, B_{accSum}PAHs would show a possible positive correlation with NO_3^- (PC2), as well as UVPM and eBC (PC3); while an inverse relationship would be

observed for SO_4^{2-} and NH_4^+ (PC2). In contrast to results obtained for PM_{10}-bound PAHs bioaccessibility rates using Gamble's solution (Sánchez-Piñero et al., 2021a), the hindering effect on B_{accSum}PAHs caused by PAHs adsorption in PM carbonaceous particles (eBC and UVPM) seems not to occur with $PM_{2.5}$-bound PAHs bioaccessibilities when ALF solution is used that might be attributed to a higher pH and presence of citric acid in ALF solution formula (Sun et al., 2016; P. Gao et al., 2019a) as previously commented, since no clear relationship with condensed ring number were found when ALF solution was used. What is more, a possible enhancing effect to B_{accSum}PAHs could be attributed to UVPM and eBC. Apart from this, possible correlations between B_{accSum}PAHs and water-soluble major ions could be also accounted, observing both hindering and enhancing effects.

Regarding the hindering effect, SO_4^{2-} and NH_4^+ could reduce PAHs dissolution in bioaccessible fractions due to SLF's saturation by their presence in solution (Caboche et al., 2011; Sysalová et al., 2014) as observed for Cl^-, Na^+ and Mg^{2+} for PM_{10}-bound PAHs bioaccessibility ratios assessment using Gamble's solution (Sánchez-Piñero et al., 2021a). Also, the NO_3^- boosting effect in B_{accSum}PAHs could be derived from some interactions within PAHs, making them more soluble species, as suggested by da Silva et al. (da Silva et al., 2015) for some metals. Also, although no data were found in literature, the possible enhancing effect of eBC and UVPM in B_{accSum}PAHs might be attributed to a reduction in the occurrence of dissolved organic species (because of being retained in carbonaceous particles instead of dissolving in ALF solution), promoting PAHs dissolution in ALF.

3.2.2. Principal component analysis for PAEs and OPFRs

In Table 2b are shown the main PCs and factor loadings for B_{accSum}PAEs and $PM_{2.5}$ properties, explaining 77% of the total variance by 3 principal components (PCs). B_{accSum}PAEs, UVPM, eBC, SO_4^{2-}, $C_2O_4^{2-}$, NH_4^+ and K^+ are the main contributors to PC1, explaining 41% of total variance. B_{accSum}PAEs, Cl^-, NO_3^- and Na^+ are the main contributors of PC2, explaining 25% of the total variance; while in PC3 (11% of the total variance), Ca^{2+} is the main contributor. Furthermore, in Table 2c are presented the main PCs and factor loadings for B_{accSum}OPFRs and $PM_{2.5}$ properties, explaining 82% of the total variance by 3 principal components (PCs). B_{accSum}OPFRs, UVPM, eBC and Ca^{2+} are the main contributors to PC1 (41% of the total variance); while SO_4^{2-} and NH_4^+ are the main features in PC2, explaining 26% of the total variance. Lastly, predominant contributors to PC3 (15% of the total variance) are B_{accSum}OPFRs and NO_3^-.

As is shown by Table 2b, B_{accSum}PAEs are distributed between PC1 and PC2, accounting for small coefficients (0.260 and −0.398, respectively) that would suggest weak relationships between B_{accSum}PAEs and components and their main contributors, as previously observed for PAHs. Taking this limitation into account, a positive relationship would be associated to B_{accSum}PAEs with all major contributors to PC1 (UVPM, eBC, SO_4^{2-}, $C_2O_4^{2-}$, NH_4^+ and K^+), while possible inverse correlations are observed between B_{accSum}PAEs with all major contributors to PC2 (Cl^-, NO_3^- and Na^+). In addition, it can be seen from Table 2c that B_{accSum}OPFRs are distributed between PC1 and PC3, showing higher coefficients (0.542 and 0.441 in PC1 and PC3, respectively) than obtained for B_{accSum}PAEs, suggesting major role in components, and then, strong correlations with them and their main contributors. B_{accSum}OPFRs seems to be positively correlated with all major contributors to PC1 (UVPM, eBC and Ca^{2+}), whereas inverse relationships were observed with NO_3^- (PC3).

As commented for PAHs, B_{accSum}PAEs and B_{accSum}OPFRs seems to be favoured by the presence of carbonaceous particles (eBC and UVPM). This enhancing effect might be derived from the reduction of the occurrence of some organic species in dissolution because of being retained in carbonaceous particles. Also, some enhancing and hindering effects in B_{accSum}PAEs and B_{accSum}OPFRs could be attributed to the presence of some water-soluble ions due to SLF saturation (Caboche et al., 2011; Sysalová et al., 2014) or specific interactions between
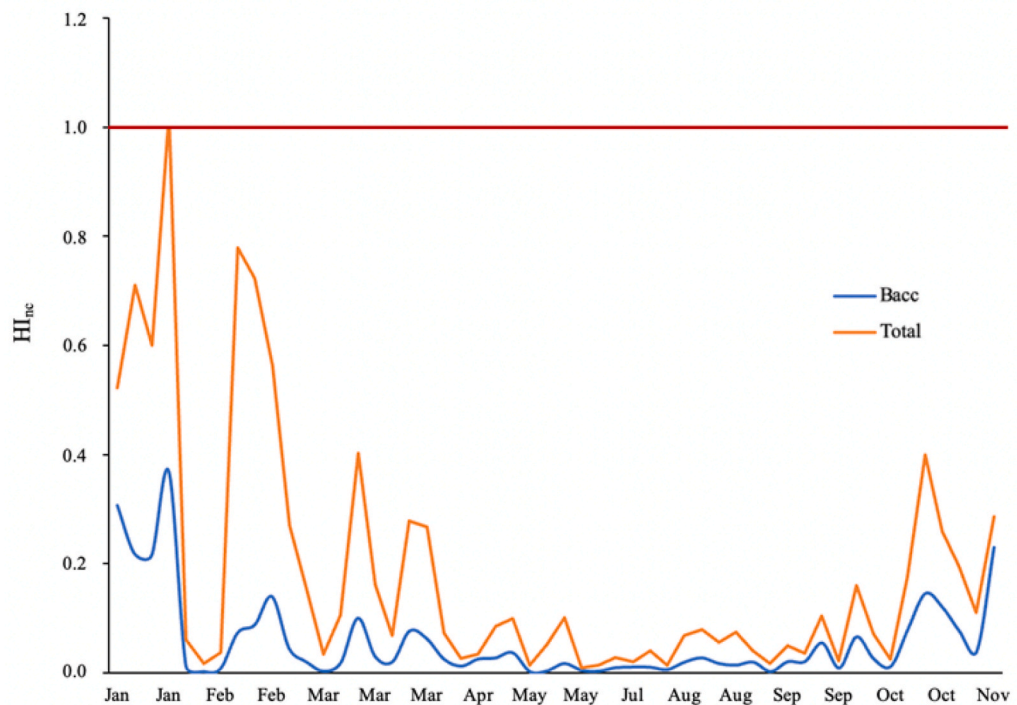
(a)
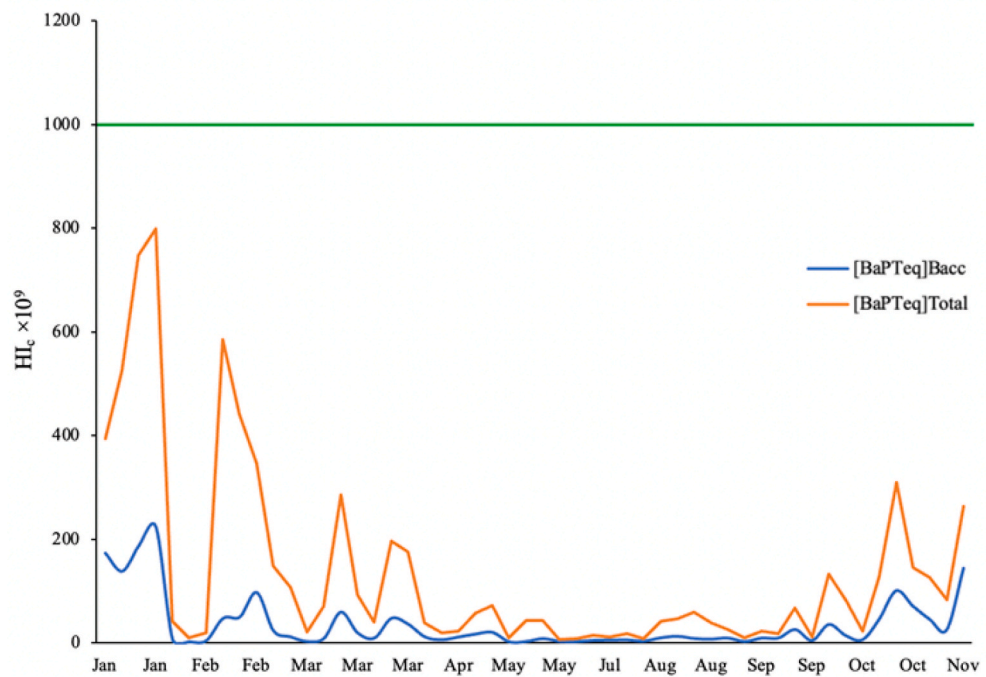
(b)

Fig. 3. (a) Carcinogenic hazard indexes (HI$_c$, by using [BaP$_{Teq}$]$_{Bacc}$ and [BaP$_{Teq}$]$_{Total}$ values) and (b) non-carcinogenic hazard indexes (HI$_{nc}$, by using bioaccessible (Bacc) and total concentrations) estimated for PM$_{2.5}$-associated PAHs via inhalation, considering the exposure scenario I for adults. The green line in the graph (a) represents the acceptable cancer risk (HI$_c$ = 1.0 × 10^{-6}), while the red line in the graph (b) represent the safe non-carcinogenic risk level (HI$_{nc}$ = 1), both set by USEPA (USEPA, 2009). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

compounds (da Silva et al., 2015), as mentioned before.

3.2.3. Principal component analysis for BPA

In Table 2d are presented the main PCs and factor loadings for $B_{acc}BPA$ and $PM_{2.5}$ properties, explaining 85% of the total variance by 3 principal components (PCs). The main features of PC1 (46%) are UVPM, eBC, SO_4^{2-}, $C_2O_4^{2-}$ and K^+; whereas PC2 is predominantly composed by Cl^-, NO_3^-, NH_4^+ and Na^+, accounted for 23% of the total variance. Finally, UVPM, eBC, $C_2O_4^{2-}$, NH_4^+ and Na^+ are the main contributors to PC3 (16% of the total variance). Attending to the table, $B_{acc}BPA$ could not be considered a main contributor of any PC since coefficients obtained are too low (0.028, −0.010 and −0.106 in PC1, PC2 and PC3, respectively), which would suggest that BPA bioaccessibility might not be influenced by any considered $PM_{2.5}$ properties/components.

3.2.4. Multiple regression

A multiple linear regression model was performed for each compound family separately, selecting $PM_{2.5}$ components and properties that seemed to correlate with B_{accSum} for each compound family as independent variables (basing on the results observed in PCAs), while B_{accSum} values were taken as dependent variables. For BPA was not performed because of having found no relationship with $PM_{2.5}$ components and properties included in the present study. As a first step, normal distribution of each considered variable was evaluated by performing a Shapiro-Wilk test, revealing that most of them were ln-normally distributed (p-value >0.05, Table S13). Different variable combinations were tested, avoiding multicollinearity between some ln-transformed predictor variables, while Bartlett's test was performed subsequently to confirm variance homogeneity (p-values <0.05 for all cases). Results suggested that no statistically significant relationships could be stablished (p-values >0.05, 95% confidence level) after fitting a multiple linear regression for any of the considered families (PAHs, PAEs and OPFRs).

3.3. Health risk assessment of PAHs in $PM_{2.5}$ samples

BaP_{Teq} values were calculated by considering total and bioaccessible fractions concentrations. A total of 12 and 3 exceedances of the BaP limit set in 1.0 ng m^{-3} by European Directive (2004)/107/EC (EC, 2004) were obtained when using total and bioaccessible PAHs concentrations, respectively. Nevertheless, average annual values of 0.83 and 0.22 ng m^{-3} were obtained by using total and bioaccessible concentrations, respectively. This great reduction suggested an overestimation of carcinogenicity associated to $PM_{2.5}$-bound PAHs if total concentrations were considered instead of bioaccessible fractions.

Health risk assessment based on [BaP_{Teq}] using total and bioaccessible concentrations were performed, showing HI_c values obtained by using total ($HI_c (BaP_{Teq})_{Tot}$) and bioaccessible ($HI_c (BaP_{Teq})_{Bacc}$) concentrations in Table S14. Attending to the results shown in the table, all HI_c mean and maximum values were below the acceptable cancer risk of 1.0×10^{-6} recommended by USEPA (Davie-Martin et al., 2017; USEPA, 2009). Then, negligible cancer risk was obtained for all studied scenarios. Additionally, HI_{nc} mean and maximum values were calculated for non-carcinogenic risk assessment (Table S14) using both bioaccessible and total concentrations, which did not exceed the non-carcinogenic risk safe level ($HI_{nc} \leq 1.0$) in any case, suggesting unlikely non-carcinogenic adverse effects in the study areas basing on the scenarios considered (USEPA, 2009). As expected, HI_c and HI_{nc} values were decreased when bioaccessible concentrations were used in comparison with total concentrations. Yet, the use of bioaccessible values could provide a more realistic health risk assessment as taking into account dissolution of pollutants in simulated body fluids. Furthermore, in Fig. 3a are represented $HI_c (BaP_{Teq})_{Tot}$ and $HI_c (BaP_{Teq})_{Bacc}$ values obtained for the most conservative scenario (scenario I for adults) for each $PM_{2.5}$ sample, whereas HI_{nc} values obtained by using total and bioaccessible concentrations are shown in Fig. 3b, observing

no exceedances of accepted risk limits by the USEPA. Basing on the graph, carcinogenic and non-carcinogenic human health risk assessment overestimation of over 4-fold (by average) were observed for both when using total concentrations with respect to bioaccessible concentrations.

4. Conclusions

In the present study, multi-class organic pollutants' inhalation bioaccessibilities in a set of 52 p.m.$_{2.5}$ samples collected at an industrial site of Vigo city were estimated. The highest inhalation bioaccessibility value was found for BPA with an average of 83%; followed by OPFRs concerning TPPO, TCPP and TiBP (accounting for 77%, 67% and 61%, respectively) and PAEs comprising DnHP and DOP (accounting for 44% and 38%, respectively). Among PAHs, Ret and Pyr shown the highest and lowest bioaccessibility values (66 and 22%, respectively); while the remaining PAHs shown bioaccessibilities ranging between 41 and 24% (Phe and DBahA, respectively). Additionally, no correlation between $logK_{ow}$ (i.e., hydrophobicity) and inhalation bioaccessibilities was found for PAHs, whereas an inverse relationship was observed for BPA, OPFRs and PAEs. Results from PCA would suggest a possible positive relationship between $B_{accSum}PAHs$, $B_{accSum}PAES$ and $B_{accSum}OPFRs$ and $PM_{2.5}$ carbonaceous content (eBC and UVPM). However, both positive and inverse correlations between $B_{accSum}PAHs$, $B_{accSum}PAEs$ and $B_{accSum}OPFRs$ bioaccessibilites and some major ions associated to $PM_{2.5}$ would be accounted. Furthermore, no relationships with none of considered $PM_{2.5}$ properties and BPA bioaccessibility were observed. Finally, a human health risk overestimation of over 4-fold (by average) was accounted when using total concentrations in comparison to bioaccessible concentrations for the most conservative scenario. Still, both carcinogenic and non-carcinogenic risks for $PM_{2.5}$-associated PAHs via inhalation in the area during the sampling campaign were within the safe level for all considered exposure scenarios.

5. Limitations of the study

The present research has some limitations comprising PBET conditions, health risk assessment and relationship between bioaccessibility and $PM_{2.5}$ properties, which are outlined in this section. As for bioaccessibility inhalation methods, the lack of standardization might lead to inappropriate assumptions derived from data comparison with literature, so many authors are calling for focus on them. Concerning health risk assessment, since no $PM_{2.5}$ deposition ratio in lungs were found, this study assumes that 100% of inhaled $PM_{2.5}$ will be in contact with alveolar fluids, which could lead to risk overestimations. Then, inclusion of other parameters such as deposition rate in the alveolar region, clearance rate and absorption of pollutants in alveolar barrier (i.e., bioavailability) should be included to attain more realistic assessments; whereas further research concerning toxicological data of PAES, OPFRs and bisphenols (i.e., IUR and RfC values), together with RfCs for more PAHs (for non-carcinogenic risk assessment) are necessary in order to perform carcinogenic and non-carcinogenic health risk assessment via inhalation as their release in simulated body fluids (i.e., bioaccessibility) from atmospheric $PM_{2.5}$ has been demonstrated in the present study. Finally, exploration of correlations between PM properties and B_{accSum} for each compound family might not be representative for all individual compounds, while data size (most bioaccessible and total concentrations < LOQs) could be a limitation for multiple linear model studies. However, these limitations could be addressed thoroughly in future studies by considering a larger dataset and other fitting/sorting models to achieve a better description of target compounds' bioaccessibility ratios.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.119577.

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