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Full length article

Characterization of organic contaminants in hair for biomonitoring purposes

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ABSTRACT

Biological monitoring is one way to assess human exposure to contaminants. Blood and urine are often used as biological matrices, but hair is an innovative and effective tool for quantifying more biomarkers over a wider exposure window. In order to improve the use of hair in exposure assessment, this article identifies relevant compounds in the literature to investigate hair contamination. Statistical analysis was performed to correlate the physical-chemical properties of the relevant compounds and their concentration levels in hair. Phthalates, pyrethroids and organophosphate flame retardants were chosen for further study of the interpretation of hair measurements for exposure assessment. No significant correlation was found between the average concentration levels in the literature and the physical-chemical properties of the selected compounds. This work also explores the properties of hair and the analytical process that may impact the quantification of organic contaminants in hair. The sample preparation method (sampling, storage, washing) were also studied and adaptations were suggested to improve the existing methods.

1. Introduction

Human beings are exposed ubiquitously to numerous contaminants related to their daily activities, but also to the introduction of toxic chemicals used in materials and consumer products (flame-retardants, plasticizers, pesticides, conservatives, biocides, etc). The entirety of contaminants to which individuals are exposed during their lives is defined as the external chemical exposome (David et al., 2021). Exposure to these compounds occurs through different media and pathways.

It is essential to assess the level of exposure to these contaminants in a preventative measure to estimate the health risk over key populations and identify effective public actions. Indeed, certain organic contaminants present in the environment are responsible for toxic effects; for example, flame retardants, plasticizers or pesticides have endocrine disrupting properties leading to effects on the immune, metabolic, reproductive and neurological systems (Chen et al., 2019; Lehmann et al., 2018). Some pesticides, for example pyrethroids, are also known for being neurotoxic and for having a negative impact on the fetal development (Andersen et al., 2022).

The monitoring of contaminants is carried out either indirectly

through their measure in the environment (bottom-up approach), or directly through the measure of relevant exposure biomarkers in biological matrices (top-down approach) (Pelletier, 2017). These two approaches provide complementary information but only the body burden gives rise to the overall assessment of exposure by measuring what has entered the body. In this context, biomonitoring is a useful tool for assessing and monitoring the exposure of the general population to toxic compounds over time and space. The first biomonitoring of the general population began in the United States with the National Health and Nutrition Examination Survey (NHANES), which conducted a survey for the Centers for Disease Control and Prevention (CDC) (Angerer et al., 2007) to evaluate the risk of malnutrition. They reported the human exposure to over 100 contaminants (Kyle, 2019). The first NHANES program started in 1971 (USDHSS and NCHS, 1992) and the approach was soon adopted in Europe in 1985 with the German Environmental Survey (GerEs), with data focusing on the monitoring of heavy metals in urine, blood and scalp hair, and also organic compounds such as pesticides, polycyclic aromatic hydrocarbons (PAHs), polychlorobiphenyls (PCBs), bisphenol A (BPA) and phthalates (Schulz et al., 2007). In 1992, Germany has also produced reference values through the Human

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Biomonitoring Commission (HBM) for the German Federal Environment Agency. More recently, other European countries also investigated biomonitoring, for example through two studies in general population in France in 2006 (The French Nutrition and Health Survey (ENNS)) for the monitoring of heavy metals (Falq et al., 2011; Santé publique France, 2011; Saoudi et al., 2012) and some pesticides (Santé publique France, 2013) and in 2015 (the Esteban study as part of the French biomonitoring program) for environmental contaminants including metals, pesticides, plasticizers, solvents and flame retardants (Fillol et al., 2021), and more recently BTEX (Benzene, Toluene, Ethylbenzene and Xylene) compounds and styrene (Santé publique France, 2023). In Belgium, since 2002, the Flemish Environment and Health Study (FLEHS) monitored metals and organic compounds in blood, urine, maternal cord and hair (mercury and methyl mercury) (Schoeters et al., 2011). Other example is BIOAMBIENT in Spain in 2007 for the monitoring of heavy metals and organic substances in blood, urine and hair (mercury) (Pérez-Gómez et al., 2013).

At the European level, DEMOCOPHES is the first project launched after 2004, for the transnational comparability and reliability of human biomonitoring results, which included 17 countries, regarding the monitoring of mercury, cadmium, cotinine, phthalates and BPA. More recently in 2016, there was the Human Biomonitoring for Europe project (HBM4EU) which was a pioneering program for Europe because of the diversity of contaminants and the geographical extent of the program itself to 24 countries. Following HBM4EU is the Partnership for the Risk Assessment of Chemicals (PARC) project, which is ongoing and includes a work package on these questions.

Within these programs, the biological matrices used were often blood and urine, and hair was rarely used and when so, only for the monitoring of the exposure to heavy metals, and more often mercury (Vorkamp et al., 2023). It has been only recently used for the measure of the exposure to specific contaminants within surveys such as the Exposure and Neurotoxic Effects to Flame Retardants survey (Chupeau et al., 2022), and for the first time within a biomonitoring campaign in Europe for the evaluation of human exposure to persistent and non-persistent organic contaminants in Luxembourg (Peng et al., 2021). Its use is limited, but hair is an innovative tool to assess the internal dose of contaminant as it allows a length-dependent retrospective exposure assessment (Kintz et al., 2015), and hence a wider exposure window. This matrix is also less invasive to sample and is easier to store (Hajeb et al., 2022). Up to now, urine has been the preferred non-invasive matrix in biomonitoring campaigns, but the concentration of target analytes can be low due to the dilution caused by varying volumes (Alves et al., 2014) and it also has a limited time window compared to hair (Yin et al., 2019).

Hence, hair meets the criteria for the ideal biomonitor due to its cumulative property, the levels of different contaminants quantified in this matrix and its suspected capacity to be representative of internal and external contamination. However, because of the lack of data (preservation of the compounds of interest in hair after sampling, inter- and intra-variability within hair strands, effectiveness of the washing methods, compound concentration normalization) and the unknown limits of this matrix (small sample sizes and sampling populations limited by religious and cultural beliefs), hair is not extensively used for biomonitoring programs.

It is important to better understand the behavior of chemical compounds in hair to improve biomonitoring through this matrix. One way to achieve this goal is by profiling the type of contaminants that are more likely to be stored and measured in hair. To do so, three objectives were set i) to select chemical families of interest to investigate hair contamination, ii) to characterize the level of these contaminants in the capillary shaft and, iii) to identify analytical limits regarding the pre-treatment (sampling, storage and washing). These three combined objectives give rise to recommendations regarding the use of hair as a biomonitor.

2. Material and methods

This work was carried out in two consecutive parts.

2.1. Search strategy, article and compounds selection

This search strategy is divided into two sections: a general and a compound-focused literature review.

The first part focused on gathering general data on hair, profile which type of compounds have been previously investigated in hair to thereafter target the search strategy. A literature review was conducted, selecting articles related to the human exposure to organic contaminants via hair (from August 2012 with a literature monitoring up to September 2023). The research items used were 'hair analysis', 'hair contaminant' and 'hair contamination' (title + abstract). These were applied to the following web servers: Web of Science, SciFinder, Google Scholar and PubMed. The data retrieved from these articles were: the objective, the type of population (age group, sex, and nationality), the number of hair samples and the studied biomarkers.

The second step focused on selecting the relevant articles, and hence compounds. To do so, a four-step method has been set up as follows:

1. The list of compounds retrieved from the literature review of step 1 were compared to the ones on HBM4EU's priority list. As mentioned before, HBM4EU is the most recent biomonitoring program in Europe set up in agreement within 24 countries of the territory. The priority substances were obtained from a thorough score and ranking approach based on properties, exposure, regulations, relevance regarding the society's concern and the doability of the analysis (Vorkamp et al., 2023). Only the molecules common to both lists were retained.
2. A more extensive literature review on each family of interest was carried out to minimize the occurrence of missing data. The list of compounds along with their references was hence completed. To do so, on the aforementioned web servers in step 1, was searched 'hair + contaminant*' (title + abstract) where the contaminant* is one of the priority substances (data available from October 2021 with a literature monitoring up to September 2023). All the articles were tabulated, and data withdrawn as explained in step 1. We obtained 92 articles of interest.
3. From this list was excluded any article that did not mention human hair, but animal hair since, even though promising, there is no proof that animal hair reflects the exposure and integration of contaminants in the human hair shaft (Yang et al., 2020). Also, only studies comprising European populations in consonance with the origin of the priority substances and published during the last eleven years were included. Reviews were also excluded from the list of articles.
4. Within the 34 selected articles, all the compounds (n = 221) quantified in hair were tabulated along with the median concentration and their physical-chemical properties. The compounds were then selected based on the following criteria:
 - Their concentration in hair so as to monitor contaminants already known to be present in the capillary shaft;
 - The diversity of the physical-chemical properties in order to cover a wide range of properties;
 - The need to investigate these families due to the emergence of related data in the literature;
 - The environmental sources and pathways' (ingestion/inhalation/dermal) diversity to consider substances with different characteristics, to monitor continuous and discontinuous exposure, and hence, when selecting the final families of compounds, this was a determining criterion;
 - The doability of the analytical development within our laboratory, so as to further investigate the limits of hair through the selected compounds.

Based on these criteria, a list of compounds was identified as pertinent for analysis for the evaluation of hair as a biomonitor, and the selection of the families of compounds of interest deduced from this list. The structure scheme for this method, from the second step, combining articles selection and families of interest is presented in Fig. 1.

The aim of this work was also to identify the methods used for hair analysis, notably the pre-treatment (sampling, storage, washing), the extraction method and the analytical method used. This information was also retrieved and tabulated with the aim of gathering and comparing, when possible, the methods used among European laboratories. Indeed, reaching a consensus on the analytical methods would greatly benefit European biomonitoring programs.

2.2. Quantitative analysis to identify chemical profiles more frequently detected in hair

The incorporation mechanism of xenobiotic in the hair shaft is still unknown to this day. According to Kintz et al. (2015), drugs are brought to the hair via three pathways: blood vessels, sweat glands and sebaceous glands, but the presence of contaminants in hair can be identified either as endogenous or exogenous (Yang et al., 2020). Indeed, contaminants from the environment can be deposited on the surface of the hair (Duca et al., 2014), but the contamination pathway into the hair is still unclear to this day.

As a first step to understanding how chemical compounds are carried into the hair, we tried to infer from concentrations reported in the literature comprising our selected compounds of interest, which ones were more likely to bind to the hair structure during growth and thus be detected according to their chemical profile, that is to figure out if there exists a relation between the physical-chemical properties (molecular weight, LogP, solubility, boiling point, vapor pressure) of the compounds and their level in hair as per the literature review, beyond the exposure levels. The ultimate purpose of comparing contaminant levels in hair to the former's properties is to frame the usage of hair to identify only contaminants that can be integrated in the hair matrix.

To do so, the median concentration of the compound for each article was tabulated and when an article comprised different sample

populations, the highest value was retained to include all the compounds which were detected in hair. For molecules that were analyzed in several studies, the median of all the reported concentrations was calculated and used for the data analysis. We also classified reported molecules according to their molecular weight (MW) and LogP using a PCA (principal component analysis) followed by a HCA (hierarchical clustering analysis). Because other chemical characteristics, such as solubility and vapor pressure, were available only for a few molecules (lack of experimental values), they could not be used to profile the compounds. The compound properties were obtained from PubChem, when available. When missing, for the values of LogP, the calculated values from Chemical Book were used or calculated by hand using Rekker's method.

The data analysis proceeded in four steps, using R software:

1. The log value of each concentration was calculated to handle skewed distributions and extreme values,
2. A Principal Component Analysis (PCA) was carried out with the molecular weight (MW) and LogP included as active variables, and the log-concentration as a supplementary variable,
3. A hierarchical clustering was then carried out,
4. Anova and t-tests were performed to compare the log-concentrations reported in the different clusters.

One of the aims of this work is to make a census of the existing analytical method and provide recommendations based on the literature research. The following results will present data from the 34 aforementioned articles regarding the methods, notably the sample pre-treatment (i.e sampling, storage and washing) which tends to be universal within environmental analysis applied to hair. Compound extraction and analysis are also tabulated in the [supplementary material \(S1\)](#), though it is to be noted that both these steps are molecule- and laboratory-dependent.

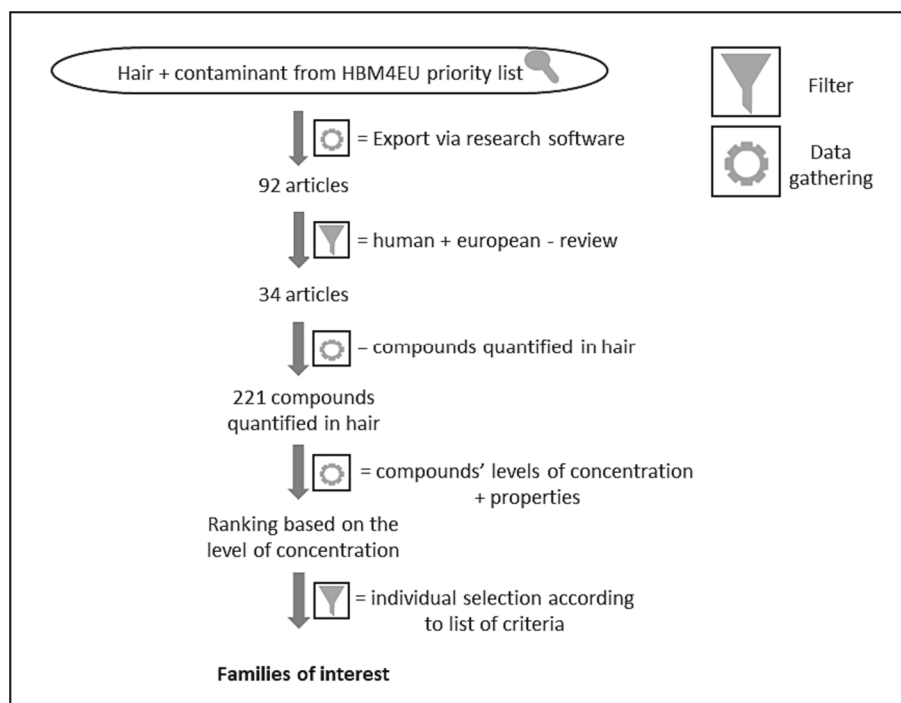


Fig. 1. Structure scheme of the pathway for articles selection and families of interest.

3. Results

3.1. Compound selection

In order to evaluate the pertinence of hair as a biological matrix for exposure to organic contaminants, it is necessary to identify compounds that are stored in keratinous matrices. In fact, the absence of certain contaminants from the hair may be related to the fact that they are not transferred to the hair shaft due to metabolism pathways and matrix affinity for specific compounds depending on their physical-chemical properties.

The reviewed literature shows an interest in the analysis of organic compounds and heavy metals in hair. The former, being the focus of this study, supposedly binds to the melanin in hair. Other than melanin, hair offers binding spots to organic molecules through its polypeptide backbone (Robbins, 2012) and interactions in its tertiary structure. Drug analysis through time has confirmed the presence of organic molecules in hair (Kintz et al., 2015). The property of organic compound integration in the hair shaft can be applied to environmental analysis since many of these compounds are carbon-chained.

From the HBM4EU priority list, we chose the following molecules for our literature review: acrylamides, benzophenones, bisphenols, organophosphate flame retardants, per-/polyfluorinated compounds, pesticides, phthalates, Hexamoll® DINCH (Di(isononyl) cyclohexane-1,2-dicarboxylate) and poly aromatic hydrocarbons (PAHs).

Over the last eleven years, we count 92 published articles comprising the analysis (review and method development) of the aforementioned compounds in hair (human and animal origin). Within these articles, only 34 of them provided data focusing on hair usage as a biomonitor in organic environmental analysis for human European populations.

221 compounds within the selected articles were detected in hair, with concentrations going from 0.002 to 50,995 pg/mg. The three most highly detected family of compounds were, in decreasing order, phthalates, organophosphates and parabens. It is noted that, with varying analytical methods, the comparison of concentrations among articles is hardly possible. Also, the use of hair samples from different populations gives rise to even more discrepancies in the quantification of certain compounds in hair.

From all the data we gathered, a final list of compounds was retained, focusing on three families: organophosphate flame retardants, phthalates and pyrethroids. Organophosphate flame retardants were selected based on their high concentration levels and the diversity of sources and pathways. Phthalates also have high concentration levels, arise from different sources and has limited literature data, especially regarding metabolites. Pyrethroids on the other hand were chosen because of the lack of data on this class of pesticides. All three families grouped present a relative diversity in their physical-chemical properties. Moreover,

laboratory expertise on these three families was an important criterion. The literature data for each family is presented below.

3.1.1. Organophosphate flame retardants

Organophosphate flame retardants are additives (Qiao et al., 2016) used to delay or stop fire propagation. They are used in Europe to replace polybrominated diphenyl ethers (PBDEs), well-known as toxic and persistent (Behl et al., 2015). However, some OPFRs have also been identified as toxic, carcinogenic and endocrine disruptors (Chen et al., 2019).

The median concentration range of OPFRs found in hair go from 0.29 to 166.6 pg/mg for the metabolites and from 8 to 2260 pg/mg for the parent molecules within 11 articles of interest (Béranger et al., 2020; Chupeau et al., 2022; Hardy et al., 2021; Hernández et al., 2019; Iglesias-González et al., 2021, 2020; Kucharska et al., 2015b, 2015a; Martín et al., 2015; Peng et al., 2021; Xu et al., 2019) out of 34 depending on the compounds (see Table 1).

3.1.2. Phthalates

Phthalates are synthetic compounds (Hsu et al., 2022) used as plasticizers and fixators (Huang et al., 2021). They are known to impact the development and reproduction system of humans (Hsu et al., 2022; Katsikantami et al., 2016).

The median concentration range of phthalates found in hair go from 0.004 to 964 pg/mg for the metabolites and from 360 to 50,995 pg/mg for the parent molecules within the 7 articles of interest (Cleys et al., 2023; Fäys et al., 2021; Katsikantami et al., 2020; Martín et al., 2019, 2016, 2015; Yin et al., 2019) out of 34 (see Table 2).

3.1.3. Pyrethroids

Pyrethroids are used as insecticides and their use has been increasing over the years (Saillenfait et al., 2015). These molecules are suspected to have neurotoxic properties and to be thyroid disruptors (Andersen et al., 2022; Saillenfait et al., 2015).

The median concentration range of pyrethroids found in hair go from 0.09 to 3.51 pg/mg for the metabolites and 0.19 to 37.93 pg/mg for the parent molecules within the 8 articles of interest (Béranger et al., 2020; Duca et al., 2014; Fäys et al., 2021; Hardy et al., 2021; Iglesias-González et al., 2021, 2020; Peng et al., 2021; Schummer et al., 2012) out of 34 (see Table 3).

3.2. Quantitative analysis to identify chemical profiles more frequently detected in hair

MW and LogP were available for the 41 molecules included in the analysis. As expected, both were positively correlated (Pearson R = 0.67). We included them both in an ACP, followed by a HCA in order to

Table 1
Concentration of organophosphate flame retardants in hair.

Nature	Abbreviated compound	CAS n°	Compound	Median concentration range (pg/mg)	Number of references
Parent	EHDPHP	1241-94-7	2-ethylhexyldiphenylphosphate	27–73	2
Parent	TBEP/TBOEP	78-51-3	tris(2-butoxyethyl) phosphate	53–114	3
Parent	TCEP	115-96-8	tris(2-chloroethyl) phosphate	15–571	3
Parent	TCP	78-32-0	tricresyl phosphate	8–87	2
Parent	TCPP	13674-84-5	tris(1-chloro-2-propyl) phosphate	1625–2260	3
Parent	TDCIPP	13674-87-8	tris(1,3-dichloro-2-propyl) phosphate	30–262	3
Parent	TEHP	78-42-2	tris(2-ethylhexyl) phosphate	12–97	2
Parent	TEP	78-40-0	Triethyl phosphate	49	1
Parent	TIBP	126-71-6	tri-iso-butyl phosphate	22–1468	3
Parent	TnBP	126-73-8	tri-n-butyl phosphate	25	1
Parent	TMCP	563-04-2	Tri-m-cresyl phosphate	10	1
Metabolite	BBOEP	298-07-7	Bis(2-butoxyethyl) phosphate	43	1
Metabolite	DEP	598-02-7	Diethyl phosphate	0.99–85.4	6
Metabolite	DMP	813-78-5	Dimethyl phosphate	0.29–166.6	5
Metabolite	DPP	838-85-7	Diphenyl Phosphate	24	1

Table 2
Concentration of phthalates in hair.

Nature	Abbreviated compound	CAS n°	Compound	Median concentration range (pg/mg)	Number of references
Parent	DBP	84-74-2	Di-n-butyl-phthalate	6910	1
Parent	DEHP	117-81-7	Di-2-ethylhexyl phthalate	50,995	1
Parent	DEP	84-66-2	Diethyl phthalate	15,365	1
Parent	DMP	131-11-3	Dimethyl phthalate	360	1
Metabolite	5-cx-MEPTP	1684398-42-2	Mono(2-ethyl-5-carboxypentyl) terephthalate	46	1
Metabolite	6-cx-MPHxP	N/A	Mono-(propyl-6-carboxyhexyl) phthalate	12	1
Metabolite	6-OH-MPMxP	N/A	Mono-(propyl-6-hydroxyheptyl) phthalate	10	1
Metabolite	MCOP	898544-09-7	Mono(carboxyisooctyl) phthalate	24	1
Metabolite	7-OH-MINP	N/A	Mono -hydroxy-isononyl phthalate	25	1
Metabolite	MBzP	2528-16-7	Mono benzyl phthalate	0.4–31.7	3
Metabolite	MECPP	40809-41-4	Mono(2-ethyl-5-carboxypentyl) phthalate	0.06–30	2
Metabolite	MEHHP	40321-99-1	Mono (2-ethyl-5-hydroxyhexyl) phthalate	25.9–50	2
Metabolite	MEHHTP	1684398-38-6	Mono (2-ethyl-5-hydroxyhexyl) terephthalate	2.7–11	2
Metabolite	MEHP	4376-20-9	Mono 2-ethylhexyl phthalate	12.1–203	3
Metabolite	MEHTP	155603-50-2	Mono(2-ethylhexyl) terephthalate	50–964	2
Metabolite	MEOHP	40321-98-0	Mono(2-ethyl-5-oxohexyl)phthalate	0.11–33	2
Metabolite	MEP	2306-33-4	Mono ethyl phthalate	7.9–822.1	5
Metabolite	MiBP	30833-53-5	Monoisobutyl phthalate	44.4–103	2
Metabolite	MnBP	131-70-4	Mono n-butyl phthalate	19.5–97	2
Metabolite	oxo-MPHP	N/A	Mono(2-propyl-6-oxoheptyl)phthalate	0.004	1

Table 3
Concentration of pyrethroids in hair.

Nature	Compound/ Abbreviated compound	CAS n°	Compound	Median concentration range (pg/mg)	Number of references
Parent	Cypermethrin	52315-07-8	[cyano-(3-phenoxyphenyl)methyl] 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate	0.19–1.09	4
Parent	Permethrin	52645-53-1	(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate	10.8–37.93	5
Parent	λ-Cyhalothrin	68085-85-8	[(R)-cyano-(3-phenoxyphenyl)methyl] (1S,3S)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate	5.68	1
Metabolite	3-PBA	3739-38-6	3-phenoxybenzoic acid	0.27–2.36	6
Metabolite	Cl2CA	55701-05-8	3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid	0.92–3.51	5
Metabolite	ClCF3CA	74609-46-4	3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid	0.09	2

classify molecules according to these physical–chemical characteristics (Fig. 2).

The first factor of the PCA was positively correlated with MW and LogP ($R = 0.91$) and ranked molecules from low (negative coordinates) to high (positive coordinates) MW and LogP. The second one allowed to distinguish molecules with higher MW (positive coordinates) or higher LogP (negative coordinates). Four clusters of compounds were identified and represented in the factorial plan, Fig. 2 (right). The first cluster (blue) included 10 compounds (parent molecules and metabolites from the three families), characterized by low MW and LogP, the second (yellow) included 6 organophosphate flame retardants (parent molecules and metabolites), characterized by lower LogP, but relatively high MW. The third cluster (grey) included 18 compounds (parent molecules and metabolites from organophosphate flame retardants and phthalates) with medium MW and LogP, compared to the others and the fourth cluster (pink) included 7 compounds (parent molecules from the three families) characterized by both higher MW and LogP.

3.3. Association between chemical characteristics and reported concentrations

Both MW and LogP were not correlated with the log-concentration (Pearson $R = -0.02$ ($p = 0.92$) and 0.045 ($p = 0.78$)). We did not find significantly different mean concentration levels in the four clusters of chemicals (Anova Fisher test: $p = 0.66$, Fig. 3), as intra-class variances were much higher compared to the inter-class variance (inter/intra variance ratio = 0.18).

3.4. Sampling

Hair grows of approximately 1 cm per month (Wolfram, 2003), meaning that 1 cm of growth represents one month of life. For example, in the case of a pregnant woman, 9 cm of hair from the skin will represent her exposure to contaminants during her pregnancy. Since hair is exposed to the external environment, it is contaminated by the latter. The sampling process needs to take into consideration the time of exposure we wish to assess. It should also be done in a way to avoid any further contamination of the sample.

There is a universal sampling method which consists of sampling a paper-thick piece of hair at the top of the vertex of the head (Kintz et al., 2015) and closest to the scalp as possible. It needs to be done using a pair of stainless steel or ceramic scissors previously washed with acetone. The sampler needs to also wear nitrile gloves to prevent any contamination (Astolfi et al., 2020). The sampling is usually done at the posterior vertex since it is the region where hair growth varies the least (Salomone et al., 2016). However, sampling at the vertex instead of the occipital region limits sampling for aesthetic purposes. Fig. 4 illustrates the region and the percentage of each sampling region in the literature within the 34 articles.

3.5. Storage

Between the sampling and the washing, the sample needs to be stored so as to avoid altering the contaminant content of the hair. For organic contaminants, aluminum paper can be used. Hair needs to be

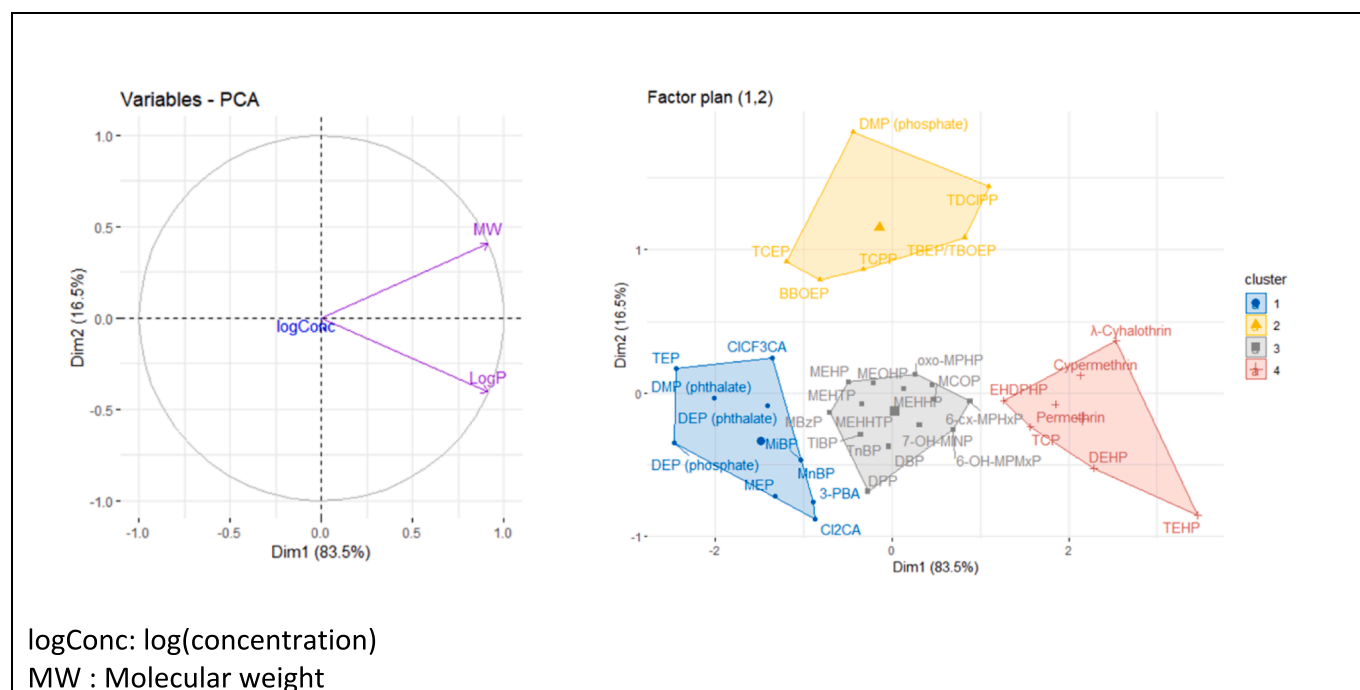


Fig. 2. PCA and Clustering of compounds according to their chemical characteristics (MW and LogP) and correlations with concentrations reported in the literature (logConc).

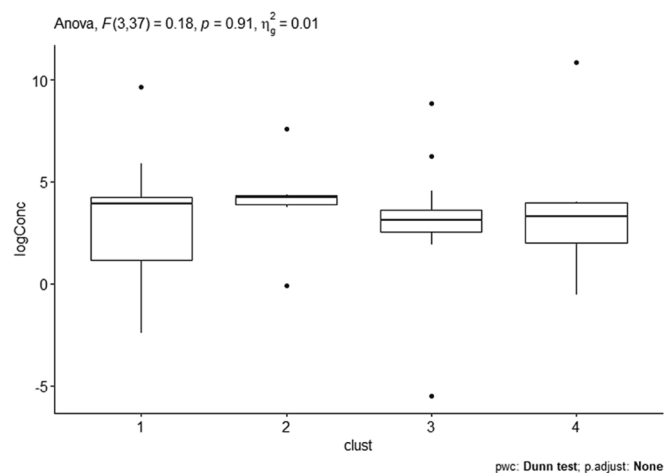


Fig. 3. Comparative distributions of log-concentrations in hair reported in the literature (logConc) according to the cluster of physical-chemical properties of the molecules (MW and LogP).

stored in a dark place so that the hair sample is not exposed to light which may result in the alternation of its protein and lipid content (Robbins, 2012). Storage at ambient temperature is also advised.

There are no guidelines on the storage of hair. The literature (Izydorczyk et al., 2020; Lin et al., 2019; Palazzi et al., 2019; Peng et al., 2020; Ramírez Fernández et al., 2020) suggests a two-step storage method:

1. Place the hair strand in aluminum foil, and then in an envelope;
2. Store the envelope in the dark at room temperature or in a freezer ($-20\text{ }^{\circ}\text{C}$ to $-80\text{ }^{\circ}\text{C}$).

Fig. 5 illustrates the storage parameters presented in the 34 selected articles. It is noted that most storage techniques follow the aforementioned protocol. Samples that were stored in paper envelope or

aluminum foil were considered to be stored in low light intensity.

3.6. Washing

Hair washing before analysis is a regularly applied and questioned step. To our knowledge, there is no referenced method for hair decontamination.

The purpose of washing is to get rid of external contamination by eliminating any deposit that may generate a matrix effect during analysis. The deposit may be dust (Duca et al., 2014), cosmetics, sweat, sebum and other surface deposits (Tobin, 2005). Washing also allows distinguishing between internal and external contamination in the case where 'non-swelling' solvents are used (Kintz et al., 2015) and the residual washes are analyzed. There are three parameters to consider when issuing a washing protocol of hair: the washing solvent, the frequency and the duration of washing, and the use of agitation or sonication. Within the literature, aqueous solvents were used as first washing solvents and organic solvents were only introduced at the second and third washes. Most articles (86 %) did two washes while less than half (46 %) proceeded with a third wash. The median time of each washing procedure, when specified ($n = 12$), is 5 min.

No normalized washing technique exists regarding the analysis of organic contaminants. The lack of data on the incorporation mechanism and the few comparative studies on different washing techniques participate in the disparities between the techniques used.

Fig. 6 shows the various washing techniques within 30 of the 34 articles, 4 of which a washing procedure was not performed. The washing procedure for each article is detailed in S1.

3.7. Extraction and analysis

As mentioned before, analytical methods vary greatly depending on which compounds are being analyzed, but also on the available equipment.

The extraction of hair is usually performed on 50 mg of hair when pulverized and 200 mg when cut into pieces. The most common extraction technique is the solvent extraction whereby hair samples are

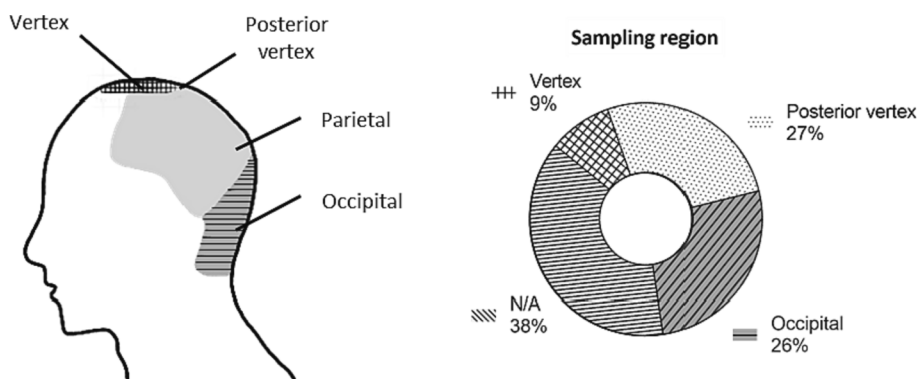


Fig. 4. Sampling regions (left) and percentage of articles sampling at these sites (right) within the articles of interest.

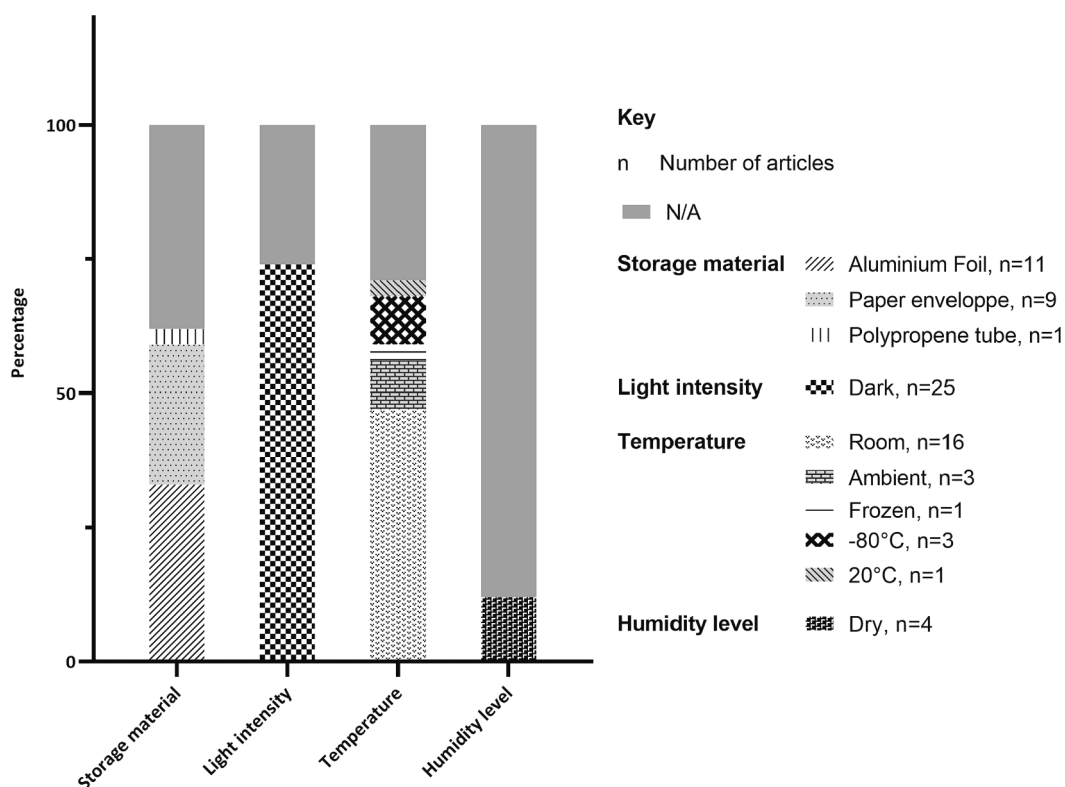


Fig. 5. Storage parameters of hair samples within the articles of interest.

incubated in a solvent of choice.

Solid Phase Microextraction (SPME) is also often performed for hair analysis. In S1 is the summary of the sample weight, the extraction technique, the analytical technique, the number of samples and the type of population studied within the 34 selected articles.

4. Discussion

4.1. Compound selection

Often, the choice of contaminants for hair analysis is based on the interest for a group of compounds or the emergence of a group of contaminants. Since hair is a keratinous matrix that does not have the same structure and properties as other biological matrices (for example blood or urine), the interpretation of the exposure level via this matrix is still uncertain. Even though numerous studies have focused on the optimization of environmental analysis to quantify the level of exposure through biomonitoring, certain questions have been omitted while

choosing contaminants as biomarker: how are we certain that these compounds are incorporated in hair? How are they metabolized and stored in the keratinous matrix?

Analyzing compounds without the certainty of their incorporation in hair may deliver false results as to their presence (or absence) and their levels. It is safer, as long as the incorporation mechanism is unknown, to analyze hair along with blood and/or urine (depending on the nature of the compounds) for better interpretation and room for correlation. When compared to blood (whole blood, serum or plasma), for pesticides (Çelik et al., 2021), brominated flame retardants (Qiao et al., 2018; Zheng et al., 2014), the correlation tends to be insignificant, but not for polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-p-furans (PCDD/Fs) (Li et al., 2020). The correlation between urine and hair has been studied more in depth, showing that urine and hair do not provide the same information, due to their different time window and the metabolic pathways of the studied contaminants (Hardy et al., 2021). Appenzeller et al. (2017) were the first to study hair along with blood and urine in rats, confirming the usage of hair as a biomonitor for

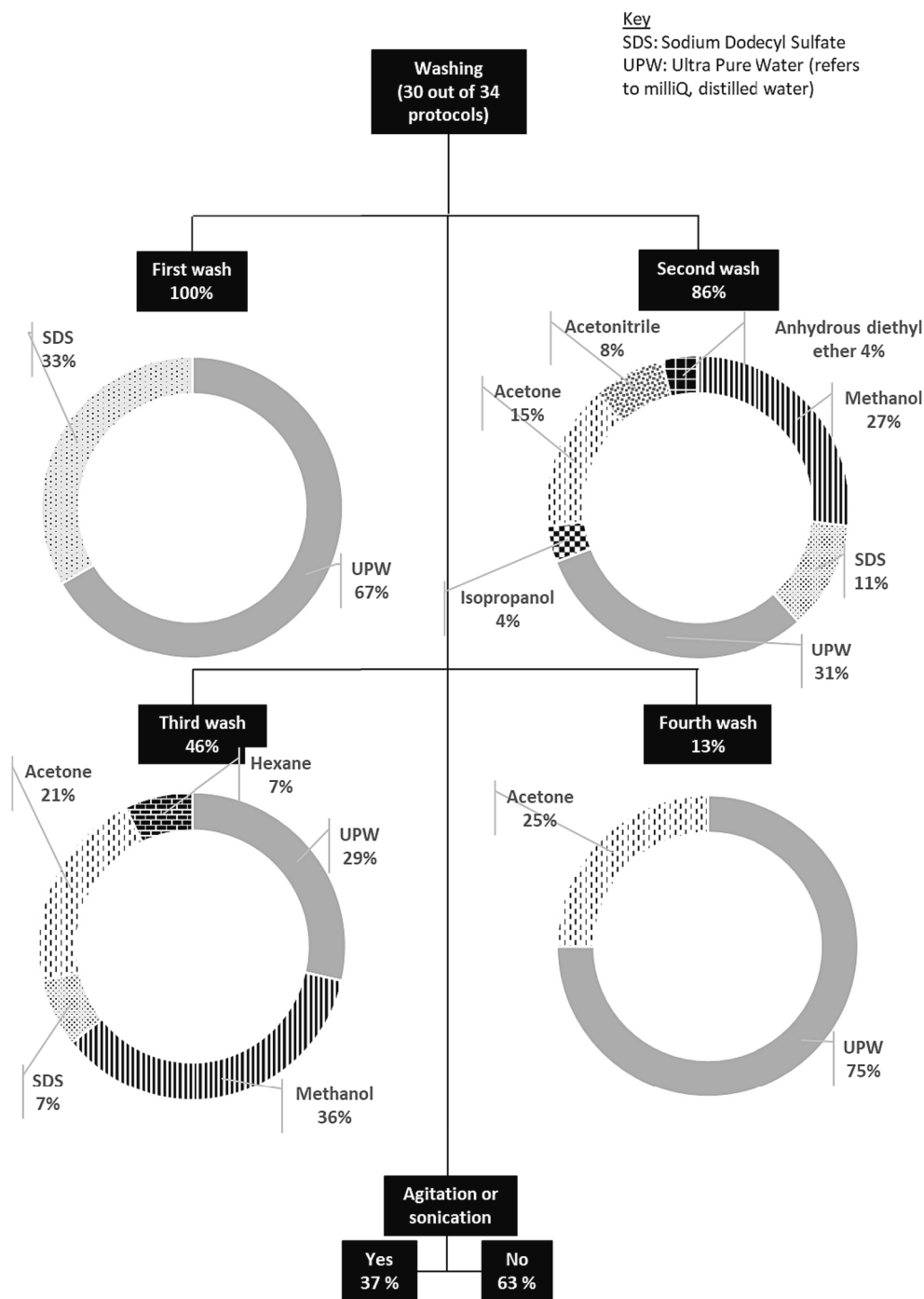


Fig. 6. Washing techniques for hair pre-treatment within the articles of interest.

pesticide exposure. Although a few following studies have analyzed all three matrices (Amir et al., 2021; Xu et al., 2019), the distribution and affinity of contaminants for a specific matrix is still unclear. However, the literature shows that hair is a potential biomonitor, and can complement the data provided by blood and urine regarding exposure.

Moreover, the comparison of the levels of contaminants in hair can be a first step towards the identification of chemical properties (LogP, molecular mass, hydro-phobic or-hilic properties) that may favor their fixation, and hence their detection in the hair matrix. However, the data analysis carried out has several limits. First of all, the median concentration levels within the same family of molecules among studies, and among the entirety of molecules, vary a lot. This is due to the different types of populations (varying age, sex and residence) studied, the

varying exposure to contaminants and the analytical paths undertaken. Indeed, over the last eleven years, the analytical techniques have improved and the sensitivity along. Hence, the median concentration of each compound within the articles of interest is not representative of the level found in hair. Moreover, not all the compounds were measured in all the studies, so that variability in reported concentrations may not only be due to analytical disparities, but also to different levels of exposure in the studied populations. This situation limits the possibility to relevantly compare the detectability of the different compounds. Second, the lack of experimental data regarding the chemical properties of the studied compounds reduced considerably the possibility to identify properties that may favor incorporation and detection in the hair.

Our final quantitative analysis has to be considered as a

methodological suggestion to evaluate the correlation between the compound properties and the level present in hair in further studies where the different compounds are measured from the same population, following a common analytical path. In order to even improve this study and better interpret the levels of contaminant found in hair, a comparison with other complementary matrices such as blood and urine can be carried out to better understand the distribution of contaminants within the human body after exposure.

4.2. Sample pre-treatment

The purpose of having a uniform sample pre-treatment is to be able to compare contaminant concentration values among populations. However, a few parameters were omitted during the optimization of the pre-treatment, some of which are suspected to have non-negligible effects.

For the sampling procedure, the hair at the back of the head is often used for sampling, but the exact region is rarely mentioned. Zhang et al. (2023) have distinguished the nape from the occipital region, and it would be beneficial to mention the precise region when sampling. Regarding the occipital region, our hypothesis is that hair at this region is often less exposed to external contaminants than the hair at the vertex. Indeed, hair in the occipital region is more shielded from sunlight which, like bleach, is also a source of oxidation of the hair matrix (Robbins, 2012), even though to a lesser level. To our knowledge, there are no comparative studies for the sampling region on the head. It would also be interesting to compare other body hair to hair.

Regarding the storage parameters, two factors are too often neglected, namely: the humidity level and the storage temperature. The concentration of compounds in hair are expressed over the sample weight. However, the humidity level affects hair's physical properties such as its mass, whereby the approximate moisture content increases with the relative humidity (Robbins, 2012). It is essential to stabilize hair weight in a humidity-controlled room before weighing and analysis. Certain articles (Katsikantami et al., 2020; Salquèbre et al., 2012; Schummer et al., 2012; Tzatzarakis et al., 2014) mentioned a light drying in the oven after washing. It is important to note that hair dried in the oven (even at low temperatures) or with an air-dryer (artificial heat) will not have the same level of humidity as air-dried hair (Watt et al., 2009). In order to minimize the effect of hair humidity and hence hair weight, it is essential to either place them in a humidity-controlled room before analysis, or to conduct all experiments in the same room where hair is stored. Regarding the storage temperature, we question whether the level of volatile and semi-volatile compounds in hair is stable when stored at this temperature. Since there is not enough data on the stability of compounds in hair, it is safer to apply the same storage conditions as other matrices. Hence, as other articles, we encourage the freezing of hair. However, the sampling date and the duration of storage have to be taken into account. Further studies on this parameter still need to be carried out.

Prior to washing hair for decontamination, it would be interesting to understand what interactions there are between hair and the deposited compounds and the location of the contaminants incorporated in hair. Due to all the uncertainties and questions on hair washing, a few decide to not wash the hair at all (Alves et al., 2014). We can assume like Polledri et al. (2020) that daily hygienic habits suffice to eliminate a certain level of contaminants. Kucharska et al. (2015b) (flame retardants) even suggested, after testing different washing solvents, to not wash the hair due to the uncertainties concerning the level of extraction when decontaminating the hair sample. However, in the absence of washing procedure, there may still be an important matrix effect due to the presence of sebum, sweat and cosmetic products.

Baumgartner and Hill (1993) have proposed a compartment theory regarding hair. They identified 'swelling and non-swelling solvents'. As explained, swelling solvents penetrate and swell the hair. Hence, they suspect that certain solvents have the capacity to extract compounds

further than the surface since they can enter the matrix. Water for example is listed as a solvent that can penetrate hair and cannot be considered, through this hypothesis, as a non-swelling solvent. For drug analysis that also comprise the detection of organic compounds, Kronstrand et al. (2015) advise using a 'non-swelling solvent' for the first wash and perform the extraction using water. There are also other parameters to consider during the washing of hair. The order of the washes may impact the levels of compound quantified, related to the degree of possible contaminant extraction during the washing procedure. The duration of washing needs to be short if a swelling solvent is used so as to reduce the extraction effect. The frequency of washing needs to be evaluated with the presence of contaminants in the washing residues. Finally, whether agitation should be used is still unclear even though it would theoretically maintain a passive diffusion, active. Whether a washing procedure for hair decontamination is needed is still unclear. We recommend carrying out preliminary tests to evaluate if there is a significant difference in the concentration of the analyzed compounds before and after washing.

For the extraction and analysis of the contaminants, the analytical techniques are often laboratory dependent. Solvent extraction is the preferred route for hair, but there is no information on the level of penetration of the solvent during washing or extraction.

5. Conclusion

Hair, even though an innovative matrix for exposure assessment, is limited in its use within biomonitoring campaigns due to the lack of data on this matrix. The main challenge regarding hair analysis is to understand how compounds are integrated into the capillary shaft. This work has provided a preliminary approach to profile which compounds are more likely to be retained, but more studies need to be carried out on the comparison of hair to other complementary matrices such as blood and urine, in order to comprehend the contaminant pathway and integration level in hair. We also believe that the standardization of hair pretreatment techniques (sampling, storage, washing) is necessary in order to provide comparable data and hence supply the data library on the level of contaminants in hair. Moreover, more work still needs to be carried out to make up for the physiological variations within the sampled population. Hair analysis is well-adapted for biomonitoring, but there is still room for improvement within the analytical pathway.

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CRediT authorship contribution statement

Ashna Lallmahomed: Data curation, Methodology, Writing – original draft. **Fabien Mercier:** Methodology, Supervision, Writing – review & editing. **Nathalie Costet:** Data curation, Methodology, Writing – review & editing. **Clémence Fillol:** Writing – review & editing. **Nathalie Bonvallet:** Methodology, Writing – review & editing, Supervision. **Barbara Le Bot:** Methodology, Project administration, Supervision, Writing – review & editing.

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.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108419>.

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