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Polycyclic aromatic hydrocarbon (PAH) exposure among European adults: Evidence from the HBM4EU aligned studies

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are persistent environmental pollutants with well-documented associations to adverse health effects, posing significant public health challenges across Europe. Human exposure to 13 urinary PAH metabolites was assessed in a harmonized cohort of European adults aged 20–39, representing diverse geographic regions across Europe: North (Iceland and Denmark), East (Poland and the Czech Republic),

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South (Croatia and Portugal), and West (France, Germany, Switzerland, and Luxembourg). This study aimed to achieve a unified understanding of PAH exposure by employing stringent participant selection criteria and harmonizing biomarker analyses by utilizing high-quality analytical protocols across multiple laboratories in Europe. Key findings revealed consistently elevated metabolite levels in smokers compared to non-smokers, with naphthalene metabolites dominating the profiles over phenanthrene and fluorene derivatives. Country-specific analyses highlighted Poland as having the highest naphthalene metabolite concentrations, while Luxembourg exhibited elevated pyrene metabolite levels. Urbanization influenced exposure, with slightly higher metabolite concentrations in town populations compared to rural areas. While sex-based stratification revealed no marked differences, gender emerged as a significant covariate in regression models, with women generally displaying higher exposure to naphthalene metabolites. Educational level further stratified exposure, with lower education correlating with increased PAH levels. Multivariate linear regression identified key exposure factors, including sampling season (i.e., summer, winter, autumn, and spring), dietary habits e.g., smoked foods, and proximity to smoke-prone environments. This dataset provides a significant baseline for evaluating the European Commission's Chemicals Strategy for Sustainability (CSS) and underscores the utility of harmonized human biomonitoring studies in informing targeted public health interventions.

List of abbreviations

1-OHNAP	1-hydroxynaphthalene
2-OHNAP	2-hydroxynaphthalene
1,2-DHN	1,2-dihydroxynaphthalene
2-OHFLUO	2-hydroxyfluorene
3-OHFLUO	3-hydroxyfluorene
9-OHFLUO	9-hydroxyfluorene
1-OHPHEN	1-hydroxyphenanthrene
2-OHPHEN	2-hydroxyphenanthrene
3-OHPHEN	3-hydroxyphenanthrene
4-OHPHEN	4-hydroxyphenanthrene
9-OHPHEN	9-hydroxyphenanthrene
1-OHPYR	1-hydroxypyrene
3-OHBAP	3-hydroxybenzo[a]pyrene
AM	Arithmetic Mean
BMI	Body Mass Index
CH	Switzerland
CZ	Czech Republic
DE	Germany
DK	Denmark
ECHA	European Chemicals Agency
ED	Endocrine Disruptors
EU	European Union
GM	Geometric Mean
FR	France
HBM	Human Biomonitoring
HBM4EU	European Human Biomonitoring Initiative
HBM-GVs	Human Biomonitoring Health Guidance Values
HMW	High Molecular Weight
HR	Croatia
IS	Iceland
LMW	Low Molecular Weight
LU	Luxembourg
P05	5th Percentile
P25	25th Percentile
P50	50th Percentile
P75	75th Percentile
P90	90th Percentile
P95	95th Percentile
PAHs	Polycyclic aromatic hydrocarbons
PL	Poland
PT	Portugal
RH	Relative Humidity
SVHC	Substances of Very High Concern
US EPA	Environmental Protection Agency of the United States of America
VIF	Variance Inflation Factor

1. Introduction

Polycyclic Aromatic Hydrocarbons (PAHs) present a unique challenge in environmental and public health due to their exceptional stability and resistance to biodegradation (Chen et al., 2019, Jesus et al., 2022). They are formed through the incomplete combustion of fossil fuels, transportation emissions, various high-temperature processes such as heating, and a wide range of manufacturing and human being activities, including the production of paints, pharmaceuticals, plastics as well as insecticides and pesticides (Umweltbundesamtes, 2007, Abdel-Shafy and Mansour, 2016, Aydin et al., 2014, Landis et al., 2019).

The phase in which these substances can be encountered depends on the environmental conditions, i.e., temperature and humidity (Ravindra et al., 2008, Li et al., 2011, Amarillo and Carreras, 2016). Lighter PAHs ($\leq$3 aromatic rings) are dominant in the summer period and heavier ones ($\geq$4 aromatic rings) in the winter months (Nguyen et al., 2018). PAHs with more than four aromatic rings are typically adsorbed onto particulate matter forms and are less likely to evaporate due to their low volatility. On the other hand, lighter PAHs are more volatile, with low vapor pressure, and can be encountered in the gaseous phase (Kameda et al., 2005, Kameda, 2011, Dat and Chang, 2017, WHO, 2010, Soleimani et al., 2022).

The ubiquity of PAHs in both indoor and outdoor environments underscores the pervasive nature of human exposure through daily activities (Falcon-Rodriguez et al., 2017). Their comportment in the ecosystems relies on interactions with other contaminants, the interblend with numerous media including soil, dust, biota, air, and water, among others as well as the occurrence of photochemical transformations (Delgado-Saborit et al., 2010, Zhong and Zhu, 2013, Zhu et al., 2009, Mannino and Orecchio, 2008, Cao et al., 2019). For instance, sunlight and reactive species such as hydroxyl radicals, ozone, and nitrogen oxides induce photochemical reactions of naphthalenes in the atmosphere and environmental systems (Arey and Atkinson, 2003). One of the primary sources of PAH exposure is dietary intake, particularly through the consumption of smoked and grilled foods (Sampaio et al., 2021, Akpambang et al., 2009).

PAHs have been categorized as toxic for human health leading to a range of adverse health outcomes (Mallah et al., 2022). Exposure to PAHs presents an elevated risk to reproductive health, especially during prenatal and postnatal periods, and may function as endocrine disruptors by inhibiting androgen functions (Ramesh and Archibong, 2011,

Zhang et al., 2016, Kakavandi et al., 2023). Given that only samples from individuals of reproductive age were included in the participant recruitment for this study. The adverse outcomes depend on factors such as the concentration of uptake, the composition of the PAHs mixture, the duration and route of exposure, as well as the age and clinical condition of the individual (Hartwig, 2013). Last but not least, occupational exposure (dermal and inhalation (Jongeneelen, 2014, Andersen et al., 2018)) to high concentrations of PAHs mixtures is associated with health effects such as inflammation, lung and laryngeal cancer, skin irritation as well as skin cancer (Du et al., 2024, Zhou et al., 2021, Kim et al., 2013, Sun et al., 2021).

The European Commission has adopted a regulation (1272/2013) which restricts PAHs in plastic and rubber products with skin or oral contact to 1 mg/kg (0.0001 % by weight). Restricted PAH-list includes Benzo[a]pyrene, Chrysene, among others. Consequently, a gradual decline in exposure levels, particularly in more recently collected samples, is anticipated. The sampling date is therefore expected to be a statistically significant variable in the models to be developed. Furthermore, it is important to highlight the initiation of discussions within the European Union (EU) and the European Chemicals Agency (ECHA) concerning the classification of PAHs as Substances of Very High Concern (SVHC), with plans to reevaluate their status in the near future, as reported by Louro et al. (2022) and Nyström (2018). These discussions are also part of the broader follow-up on the Chemical Strategy for Sustainability (CSS) (Karakoltzidis et al., 2024, Vicente et al., 2023, Karakoltzidis et al., 2025b, Karakoltzidis et al., 2025a, Leso et al., 2024).

The primary aim of this study was to achieve a unified understanding of polycyclic aromatic hydrocarbon exposure across Europe, focusing on two heavy PAHs—pyrene (4 rings) and benzo[a]pyrene (5 rings)—and three lighter PAHs—naphthalene (2 rings), fluorene (3 rings), and phenanthrene (3 rings). This was achieved by identifying key exposure patterns and determinants of PAH exposure patterns in adults across numerous EU countries through stringent participant selection criteria and harmonized biomarker analyses, employing high-quality analytical protocols across multiple European laboratories, as part of the HBM4EU (Human Biomonitoring for Europe) initiative. Additionally, this study aims to raise awareness regarding the significance of human biomonitoring in the Chemicals Strategy for Sustainability. Finally, it underscores the importance of harmonized HBM studies in supporting evidence-based public health interventions and promoting targeted strategies to mitigate chemical exposure risks.

2. Materials and methods

2.1. HBM4EU aligned studies

The present work was part of the Aligned Studies in the frame of the European joint program, HBM4EU (Ganzleben et al., 2017). HBM4EU (Human Biomonitoring for Europe) is a research initiative that aims to improve human biomonitoring (HBM) practices across Europe. To this end, the HBM4EU Aligned Studies represent a concerted effort to harmonize HBM practices, facilitating the generation of high-quality, comparable data on human exposure to environmental chemicals. These studies are integral to the broader HBM4EU initiative, which aims to bridge the gap between science and policy by providing robust evidence to inform regulatory actions and protect public health. Conducted in alignment with a standardized protocol, the studies encompass the collection and analysis of biological matrices such as e.g., blood, urine, and hair from both the general population and targeted subgroups, including children, pregnant women, and workers in specific sectors. In the present study, urine samples collected from the general population across ten countries—namely, Iceland, Denmark, Poland, Czech Republic, Croatia, Portugal, France, Germany, Switzerland, and Luxembourg—were analyzed.

A core focus of Aligned Studies is the inclusion of priority substances identified by the experts of the HBM4EU, such as phthalates, bisphenols, pesticides, per- and polyfluoroalkyl substances (PFAS), Polycyclic Aromatic Hydrocarbons (PAHs), and heavy metals. To ensure data comparability and reliability, the Aligned Studies implement harmonized methodologies for participant recruitment, sample collection, chemical analysis, and data interpretation. Additionally, they integrate health and exposure questionnaires to link biomonitoring results with potential determinants of exposure and health outcomes. The HBM4EU-Aligned Studies offer a unique opportunity to assess geographical and temporal trends in chemical exposure, identify vulnerable populations, and investigate exposure–response relationships within a comprehensive pan-European framework aligned with the EU Chemical Strategy for Sustainability (CSS). Human biomonitoring is central to the CSS because it provides critical, real-world data about human exposure to chemicals and their potential health impacts as well as evidence-based policies for decision-making. The HBM4EU Aligned Studies design has also been described in detail in previous publications (Gilles et al., 2021, Gilles et al., 2022, Govarts et al., 2023).

2.2. Study design, sample size and population

The measurement of exposure to polyaromatic hydrocarbons was specifically chosen for the adults age group (20–39 years, n = 2,611), and included 10 countries: DK: Copenhagen Minipuberty study (parents)/Danish Young Men Study (CPHMINIPUB/DYMS), IS: Icelandic National Dietary Survey (Diet_HBM), CZ: Central European Longitudinal Studies of Parents and Children: Young Adults (CELSPAC: YA), PL: Polish Aligned Environmental Study (POLAES), HR: Implementation of Human Biomonitoring Survey In Adults in Croatia Using HBM4EU Methodology (HBM in Croatia), PT: Exposure of the Portuguese Population to Environmental Chemicals: a study nested in INSEF 2015 (INSEFExpoQuim), CH: Human Biomonitoring for Europe Program for Switzerland (HBM4EU-study Switzerland), FR: Etude de sSanté sur l'environnement, la biosurveillance, l'activité physique et la nutrition (ESTEBAN), DE: Environmental Specimen Bank (ESB) and LU: Observation des Risques et de la Santé Cardiovasculaire au Luxembourg (Oriscav-Lux2) (Table 1). The sampling period ranged from 2014 to 2021, and the male-to-female ratio was maintained at 50:50. Furthermore, all participating studies adhered to the quality-assured and standard operating procedures for recruitment, sampling, storage, and transport established within the HBM4EU project. All participating studies received ethical approval, and every participant signed an informed consent.

2.3. Chemical analysis

Urinary samples (Table S1) from adults were collected and PAHs metabolites determination was performed in laboratories that successfully participated in the HBM4EU Quality Assurance/Quality Control (QA/QC) program (Esteban López et al., 2021, Nübler et al., 2023). Twenty-five laboratories from 12 countries achieved satisfactory results for PAHs biomarkers, and 13 biomarkers were selected for measurement in the final analysis. It is important to note that not all countries measured all biomarkers, and not all labs have used the same analytical technique. Table S1 highlights the variation of the analysis methods and biomarkers measured across partners. However, most partners adhered to the analytical method described below. Most laboratories chose high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) in negative mode for PAHs analysis in urine. The minimum urine sample quantity for all selected biomarkers was 2 ml. After spiking urine samples with ^{13}C-labeled internal standards and a sodium buffer containing β-glucuronidase/arylsulfatase (Ramsauer et al., 2011, Onyemauwa et al., 2009), enzymatic hydrolysis of conjugates was performed overnight at 37 °C, followed by the addition of acetonitrile prior to injection. In general, numerous metabolites of PAHs with the potential to serve as exposure biomarkers have already been identified (Barbeau et al., 2015, Li et al., 2008, Motorykin et al., 2015, Urbancova

Table 1
Human biomonitoring studies conducted as part of the HBM4EU Aligned Studies, focused on the assessment of Polycyclic Aromatic Hydrocarbons (PAHs) within adults.

Study name	Country	Sample type	Representativeness	European region	Reference
Icelandic National Dietary Survey, (Diet_HBM)	Iceland	Urine Spot	National	North	–
Copenhagen Minipuberty study (parents)/Danish Young Men Study (CPHMINIPUB/DYMS)	Denmark	Urine Spot	Regional	North	(Busch et al., 2021)
Polish Aligned Environmental Study (POLAES)	Poland	Urine Spot	Regional	East	–
Central European Longitudinal Studies of Parents and Children: Young Adults (CELSPAC:YA)	Czech Republic	Urine Spot/Urine first morning urine	Regional	East	(Piler et al., 2017)
HR: Implementation of Human Biomonitoring Survey In Adults in Croatia Using HBM4EU Methodology (HBM in Croatia)	Croatia	Urine first morning urine	National	South	–
Exposure of the Portuguese Population to Environmental Chemicals: a study nested in INSEF 2015 (INSEFExpoQuim)	Portugal	Urine first morning urine	National	South	–
Etude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (ESTEBAN)	France	Urine first morning urine	National	West	–
Environmental Specimen Bank (ESB)	Germany	Urine 24 h	Regional	West	(Kolossa-Gehring et al., 2012, Lermen et al., 2014, Lemke et al., 2021)
Human Biomonitoring for Europe Program for Switzerland (HBM4EU-study Switzerland)	Switzerland	Urine first morning urine	Regional	West	–
Observation des Risques et de la Santé Cardiovasculaire au Luxembourg (Oriscav-Lux2)	Luxemburg	Urine Spot	National	West	(Alkerwi et al., 2019)

et al., 2017). In this study, the following urinary PAHs metabolites were measured: Naphthalene (NAPH) metabolites: 1-,2-dihydroxynaphthalene (1,2-DHN), 1-hydroxynaphthalene (1-OHNAP), 2-hydroxynaphthalene (2-OHNAP); Fluorene (FLUO) metabolites: 2-hydroxyfluorene (2-OHFLUO), 3-hydroxyfluorene (3-OHFLUO), 9-hydroxyfluorene (9-OHFLUO); Phenanthrene (PHE) metabolites: 1-hydroxyphenanthrene (1-OHPHEN), 2-hydroxyphenanthrene (2-OHPHEN), 3-hydroxyphenanthrene (3-OHPHEN), 4-hydroxyphenanthrene (4-OHPHEN), 9-hydroxyphenanthrene (9-OHPHEN), the Pyrene (PYR) metabolite 1-hydroxypyrene (1-OHPYR), and the Benzo(a)pyrene (B[a]P) metabolite 3-hydroxybenzo(a)pyrene (3-OHBAP). Detailed information regarding the limit of detection (LOD) and limit of quantification (LOQ) for each metabolite and study, along with the parent compound of each metabolite, are provided in the supplementary material (Table S2). Lastly, it is important to emphasize that chemical analysis of PAH metabolites is not an original part of this study.

2.4. Questionnaire and additional data

The covariates for this study were obtained through the utilization of distinct questionnaires. Participating countries employed either their proprietary questionnaires or questionnaires founded on the HBM4EU questionnaire, following the harmonized approaches (Gilles et al., 2022) outlined in HBM4EU (Pack et al., 2023). Furthermore, the administration of these questionnaires to participants varied across countries, encompassing self-administered, telephone-based, in-person, computer-assisted or paper-based methods. Questionnaires were utilized to gather information on socio-demographic characteristics, dietary habits, health status, lifestyle, and residential environment in this study. They also provided details about sources of chemical exposure, the usage of consumer products, and information on recent and occupational exposures. To ensure consistency across studies, a post-harmonization approach was adopted. The finalized codebooks containing harmonized variables (Gilles et al., 2021) can be accessed online at the following link: HBM4EU Harmonized Codebook Adults-Aligned Studies on Zenodo (https://doi.org/10.5281/zenodo.6598404).

2.5. Statistical analysis

This study is part of the HBM4EU (Human Biomonitoring for Europe) initiative, which aims to harmonize human biomonitoring data across Europe to better understand chemical exposure patterns. Using data from these investigates, PAH exposure in adults across multiple EU countries is assessed. The study objectives include identifying key factors influencing PAH exposure through multivariate regression, exploring cross-country variations, and stratifying exposure by demographic factors such as smoking status, sex, education level (ISCED; Schneider (2013)), and urbanization (European Commission, 2014). These analyses aim to provide insights into population-level PAH exposure and inform targeted interventions to mitigate associated health risks. The PAH metabolites presented in this work have been measured in ten European countries. The set analyses include 1-OHNAP, 2-OHNAP, 1,2-DHN, 2-OHFLUO, 3-OHFLUO, 9-OHFLUO, 1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, 9-OHPHEN, 1-OHPYR, and 3-OHBAP. However, the number of metabolites reported varied among studies. Additionally, we included the sums of the analyzed metabolites arising from the same parent compound in those studies. These sums were Σ(1-OHNAP and 2-OHNAP), Σ(1-OHNAP, 2-OHNAP, and 1,2-DHN), Σ(2-OHFLUO and 3-OHFLUO), Σ(2-OHFLUO, 3-OHFLUO, and 9-OHFLUO), Σ(1-OHPHEN, 2-OHPHEN, and 4-OHPHEN), Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, and 4-OHPHEN), and Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, and 9-OHPHEN). To our knowledge, no other combinations of PAH metabolite sums have been identified in the literature.

For values lower than the limit of detection/quantification (LOD/LOQ), we utilized the Maximum Likelihood Estimation (MLE) methodology as it is described by EFSA (2010) and suggested as the best approach to address such matters (Fernández et al., 2021b, EFSA, 2010). It should be stated that censored data imputation was only performed if no more than 60 % of the data points were below the LOQ. To summarize the biomarkers identified in each study, we considered several parameters, including the number of participants, the LOQ value, and the quality control results, which were assured by HBM4EU QA/QC (Nübler et al., 2023). The biomarker levels of PAHs, measured in units of μg/L and the creatinine standardized levels in μg/g creatinine (O'Brien et al., 2017, O'Brien et al., 2016, Barr et al., 2005) were described using statistical measures such as the arithmetic mean (AM), geometric mean (GM) with its 95 % confidence interval (CIs), selected percentiles including 5th, 25th, 50th, and 75th, 90th, and 95th percentiles (P05, P25, P50, P75, P90, and P95), and standard deviation. Given the variety of samples (first morning urine, 24-h urine, and urine spot), creatinine-normalized values will be the primary focus of the present analysis. In

the stratification section, we also provide one-way ANOVA p-values and Cohen's (d) effect sizes for the groups that are compared. Effect sizes lower than 0.2 are considered to indicate a small effect, effect sizes between 0.2 and 0.8 indicate a medium effect, and effect sizes greater than 0.8 indicate a large effect. The value of 0.05 is considered a statistically significant value. Participants were stratified according to their country of residence, geographical region (north, south, west, east), education level (ISCED; Schneider (2013)), degree of urbanization (European Commission, 2014), and smoking status. These demographic variables were selected as the most significant among others conducting linear univariate regression tests (data are not presented here) and expert judgement. These selections are also confirmed by the multivariate linear regression modeling. For each stratification step a table with the aggregated data is presented in supplementary material with the volume-based (μg/L) and creatinine-standardized (μg/g creatinine) values. Multivariate linear regression analysis was employed to reveal the influence of multiple variables on the levels of PAH metabolites measured. The models developed were based on log-scale transformed, creatinine-adjusted levels of metabolites. To check for multicollinearity, we assessed the Variance Inflation Factor considering values lower than 5.

The statistical analysis for this study was performed using R software (R Core Team, 2009), version 4.3.0. Plots were introduced with the ggplot2 package (Wickham, 2011), and missing values were multiply imputed using the mice R-library (Van Buuren and Groothuis-Oudshoorn, 2011), adhering to the 60 % rule described earlier. Maps were generated using the tmap package (Tennekes, 2018). Particularly, the boxplot descriptors in this study include the median value at the center, with the box representing the interquartile range (IQR), which reflects the middle 50 % of the data. The whiskers extend to encompass values within 1.5 times the IQR from the quartiles. To enhance clarity, outliers have been removed; any data point below the lower bound or above the upper bound is considered an outlier.

3. Results and discussion

3.1. General characteristics of the study population

Table 2 presents descriptive statistics for all datasets included in the analysis, comprising individual data collected from all countries. Details about the harmonization of human biomonitoring studies in the framework of HBM4EU have been described earlier (Gilles et al., 2022). The table with the general characteristics of the study population per country as well as the rest of the non-dietary exposure data is provided in the supplementary material (Table S3). The study involves a diverse set of countries, each contributing to a total participant pool of 2,611 individuals. To our knowledge, this represents the largest dataset of pooled samples related to PAHs exposure in Europe thus far (Sochacka-Tatara et al., 2018, Joksić et al., 2022, Fernández et al., 2021a, Urbancova et al., 2020). Notably, pregnant women and occupationally exposed individuals were not considered in this study. The study captures a range of seasons, with data collected in winter (27.19 %), spring (15.85 %), summer (23.2 %), and autumn (33.66 %). Additionally, the sampling period spans from 2014 to 2021, indicating a comprehensive and multi-year approach to data collection. The descriptive analysis revealed a gender split of 46.8 % males to 53.2 % females. The participant age range had an overall average of 30.3 years, with slight variations observed among countries. Educational attainment was largely high across the sample, with 68.1 % achieving the highest levels of education (ISCED > 4).

The study intentionally included both smokers and non-smokers, gathering data on the number of cigarettes smoked, passive smoking exposure, and its frequency within specific timeframes before sampling (2 h and 24 h) (Table S3). It is important to note that data on exposure to combustion products, such as 'wildfires,' 'fireplaces,' 'barbecue activities,' or 'indoor use of coal/biomass burning,' was only available for 10–50 % of the participating countries, as summarized in Table S3. This variability in data availability underscores the challenges in ensuring comprehensive and harmonized data collection across all countries involved in the study. The supplementary material (Table S4) details participants' dietary habits by categorizing the patterns into six frequencies, from less than once a month to daily. BMI is crucial for evaluating health effects posed by exposure to PAHs, particularly concerning obesity and its associated risks like metabolic syndrome and type 2 diabetes. The link between PAH exposure and obesity-related health issues is stronger in individuals with higher BMI (Stallings-Smith et al., 2018, Liu et al., 2023), highlighting the need for further research to inform public health policies.

3.2. Levels of urinary PAH metabolites in the study population

The concentrations of PAH metabolites in urine samples from all countries are presented in Table 3. It provides a comprehensive overview, specifying the number of metabolites studied in all countries as well as the aggregated descriptive levels for each metabolite. Urinary concentrations are presented in μg/L, while standardized values are presented in μg/g creatinine (O'Brien et al., 2017, O'Brien et al., 2016, Barr et al., 2005, Lermen et al., 2019). In this study, our focus is on standardized urinary concentrations. This choice is driven by the heterogeneity of the HBM4EU-aligned adult studies, which encompass a mix of urine sampling methods including first-morning urine, random spot samples, and 24-hour collections. Creatinine adjustment has been implemented for improving the comparability of urinary biomonitoring data by accounting for individual variations in hydration status. This approach is also suggested by Gilles et al. (2022).

Analysis of the combined data revealed distinct exposure patterns for key metabolites, with the highest levels observed for 2-OHNAP (GM (95 % CI) 3.93 μg/g creatinine (3.82–4.16)). It is noteworthy that 1,2-DHN is discussed sparingly due to its measurement being limited to only one participating country i.e., Luxembourg ($n = 210$). Conversely, 2-OHNAP and 1-OHNAP findings align with similar investigations across Europe (Freire et al., 2009, Sochacka-Tatara et al., 2018, Murawski et al., 2020, Urbancova et al., 2020), underscoring these metabolites' prevalence in urine samples. This suggests that the European population may experience notable exposure to naphthalene (Yost et al., 2021). Naphthalene is classified by the International Agency for Research on Cancer (IARC) as a potentially carcinogenic substance, highlighting the importance of minimizing exposure to naphthalene for public health and safety. However, it is important to note that metabolite levels alone cannot directly indicate exposure levels to naphthalene or other PAHs, as different metabolites have varying excretion fractions relative to their parent compounds. Therefore, while elevated levels of naphthalene metabolites may suggest exposure, the interpretation of these levels should take into account the metabolic and excretion differences across various PAHs and deeper methodologies such as e.g., exposure reconstruction (Georgopoulos et al., 2009) should be employed. Alternatively, the metabolites of phenanthrene exhibited notably lower GMs and urinary concentrations of fluorene metabolites compared to naphthalene metabolites. Again, target methodologies should be employed to approximate fluorene intake and compare it to naphthalene. It is worth noting that the measurement of 9-OHFLUO was conducted in only two countries. Finally, it is fundamentally important to note that the low geometric mean concentration of 3-OHBAP observed across the studied countries may be attributable to limitations in the analytical methods used, rather than accurately reflecting actual levels of human exposure. Specifically, among the countries participating in this study, only Germany and France reported limits of quantification (LOQs) sufficiently low to reliably measure the minimal concentrations of 3-OHBAP (Table S2). This underscores the need to enhance the quantification methods for 3-OHBAP by further lowering the LOQs. As 3-OHBAP is a metabolite of a well-established carcinogenic PAH, even low concentrations indicate potential health risks (ECHA, 2016, EFSA, 2008).

Table 2
General Characteristics of the study population.

	North		East		South		West				All
Country	**Iceland**	**Denmark**	**Poland**	**Czech Republic**	**Croatia**	**Portugal**	**France**	**Germany**	**Switzerland**	**Luxemburg**	
Participants N	203	240	228	300	300	296	201	333	300	210	2611
Sampling season (n)											
Winter	25	2		12	121	53	50	333	67	47	710 (27.19 %)
Spring		40		119		16	49		147	43	414 (15.85 %)
Summer	71	111		89		152	42		86	57	608 (23.2 %)
Autumn	107	87	228	80	179	75	60			63	879 (33.66 %)
Sampling period											
Start Date – End Date	2019/1–2021/12	2017/2–2019/12	2017/9–2017/12	2019/3–2019/12	2019/1–2020/12	2019/1–2020/12	2014/1–2016/12	2014/1–2019/1	2020/1–2020/8	2016/1–2018/12	2014/1–2021/12
Sex (%)											
Male (Female)	43.8 (56.2)	59.6 (40.4)	30.7 (69.3)	48.3 (51.7)	47.0 (53.0)	42.2 (57.8)	40.3 (59.7)	50.2 (49.8)	54.0 (46.0)	47.1 (52.9)	46.8 (53.2)
Age (years)											
Mean (Min-Max)	30.8 (20–39)	30 (20–39)	33.5 (20–39)	27.2 (20–37)	30.6 (20–39)	34.6 (28–39)	31.9 (20–39)	23.5 (20–29)	30.8 (20–39)	33.6 (25–39)	30.3 (20–39)
Height (cm)											
Mean (Min-Max)	174 (150–201)	177 (153–198)	170 (152–196)	175 (154–202)	174 (150–197)	168 (142–190)	170 (145–194)	177 (150–198)	174 (152–203)	172 (150–197)	173 (142–203)
BMI (kg/m^2)											
Mean (Min-Max)	26.2 (16.1–51.2)	24.2 (15.8–42)	23.8 (16.8–39.2)	24 (17.4–39.3)	24.5 (17.8–41.5)	25.4 (17.7–40.8)	24 (16.5–44.7)	22.3 (16.3–34.6)	23.5 (16.3–39.5)	24.8 (17.2–42.9)	24.1 (15.8–51.2)
Method to obtain Participants' Height (n)											
Measured (Self-Reported)	0 (180)	180 (0)**	0 (228)	300 (0)	0 (300)	39 (257)	201 (0)	0 (333)	58 (242)	210 (0)	808 (1540)
Method to obtain Participants' Weight (n)											
Measured (Self-Reported)	0 (180)	180 (0)**	0 (228)	300 (0)	0 (300)	0 (257)	201 (0)	0 (333)	58 (242)	210 (0)	769 (1540)
Creatinine (mg/L)											
GM (95 CI)	1146 (1033–1270)	1228 (1114–1354)	1120 (1045–1200)	1431 (1342–1526)	1423 (1331–1521)	1153 (1088–1223)	915 (827–1013)	688 (651–727)	947 (883–1015)	1728 (1602–1863)	1128 (1100–1157)
Educational level (%)											
Low	5.9	12.5		0.7	0.3	19.9	2		1	4.8	4.6
Medium	29.1	24.6	41.7	23.3	36	36.1	31.3		23	32.9	26.8
High	63.5	60.4	58.3	75.7	63.7	43.9	66.7	100	74.7	62.4	68.1
Degree of urbanization of residence (%)											
Cities	74.9	89.2	100	71.7	58	27	48.3	100	91.3	19	69.2

(*continued on next page*)

Table 2 (*continued*)

	North		East		South		West				All
Country	**Iceland**	**Denmark**	**Poland**	**Czech Republic**	**Croatia**	**Portugal**	**France**	**Germany**	**Switzerland**	**Luxemburg**	
Towns or suburbs	11.3	9.2		10	13.7	37.2	27.4		8.7	45.2	15.4
Rural area	11.8	1.2		14.3	28.3	35.8	24.4			35.7	14.7
Employment or Unemployment of the participants (%)											
Employed		37.9 (60.0)		86 (13.3)	99.7 (0.3)	87.2 (6.8)	81.6 (18.4)		80.0 (19.3)	87.6 (12.4)	58.8 (25.2)
(Unemployed)											
Smoking Status (%)											
Yes (No)	6.9 (91.6)	8.3 (89.6)	13.2 (86.8)	12.0 (87.0)	30.3 (69.7)	24.3 (73.0)	24.9 (75.1)	9.3 (90.7)	22.0 (72.7)	17.1 (82.9)	17.1 (81.6)

*Missing values are not explicitly included in this table. Instead, they are calculated as the difference between the total number of participants considered and the sum of the values reported for each question. If this difference equals the total number of participants, it indicates that no missing values are present.
**In CPHminipuberty height was self-reported and weight was measured. In DYMS both Height and weight were measured.

Therefore, improving detection sensitivity is essential to ensure more accurate exposure assessment and enhance the evaluation of the associated risks.

3.3. Country specific exposure levels

The levels of exposure for the individual countries are elaborated in Table S5 (both creatinine-standardized and volume-based levels) in the supplementary material. Naphthalene metabolites were consistently measured across all countries in the study. Specifically, 1-OHNAP exhibits the highest values in Poland followed by Croatia and Denmark. 2-OHNAP was the metabolite with the highest concentrations across all countries, with Poland once again exhibiting the highest values. Only three countries exhibit levels below the overall GM of the study, with the lowest value observed in Germany, followed by Switzerland and Iceland. Unfortunately, 1,2-DHN was measured exclusively in Luxemburg.

Fluorene metabolites (2-OHFLUO, 3-OHFLUO, and 9-OHFLUO) were measured by several countries, though not universally, with 9-OHFLUO assessed only in 411 individuals from two countries. Seven countries contributed results for 2-OHFLUO (n = 1750). The geometric means across those countries are closely aligned, with the highest values observed in Croatia and Portugal. The lowest recorded levels were in Iceland. In accordance with this, 3-OHFLUO was evaluated in six countries (n = 1510). Geometric mean values for 3-OHFLUO are uniformly low across all countries, with the highest value observed in France, followed by Luxemburg. The lowest values are once again found in Iceland. Exclusively measured in France and Luxembourg, the last metabolite, 9-OHFLUO, exhibits varying concentrations. France reports the highest value whereas Luxembourg records the lowest.

Phenanthrene metabolites (1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, and 9-OHPHEN) were measured in most countries, showing relatively low concentrations compared to those of other metabolites. Specifically, 1-OHPHEN (n = 1843) was measured in seven countries. Portugal and France exhibit the highest values, followed by Croatia. The lowest concentrations were reported by the Czech Republic and Iceland. 2-OHPHEN was assessed in six countries, with the highest levels observed in the Czech Republic, followed by Portugal. The lowest concentration was recorded in Germany. 3-OHPHEN was assessed in seven countries, with the highest concentration observed in Luxembourg and the lowest value to be recorded in Croatia. 4-OHPHEN stands out as the phenanthrene metabolite measured in the highest number of countries (n = 8 out of 10) in the present study, with a total sample size of 2083. However, it presents the lowest geometric means among all phenanthrene metabolites. The final phenanthrene metabolite, 9-OHPHEN, was assessed in seven countries (n = 1843). The Czech Republic reported the highest value while the lowest value was found for Germany.

The pyrene metabolite, 1-OHPYR, was assessed in most of the study countries (n = 9 out of 10, sample size = 2371), with Luxembourg reporting the highest GM, reaching 0.21 (0.19–0.23) μg/g creatinine. The Benzo(a)pyrene metabolite, 3-OHBAP, was measured in six of the participating countries. Detailed information is available in the supplementary material (Table S5). See also the work of Burkhardt et al. (2023) for a specific evaluation of the German data.

3.4. Correlation analysis

The Pearson correlation matrix (Fig. 1) illustrates the relationships between logarithmically transformed, creatinine-standardized exposure biomarkers. The correlation coefficients range from 0.27 to 0.94, with stronger positive correlations represented by darker blue hues and larger circles, while weaker correlations are shown with lighter shades and smaller circles. Strong positive correlations among metabolites may be associated with similar sources of exposure and environmental co-occurrence, the CYP (cytochromes P450) enzymes involved in metabolism in general and individual factors such as enzyme induction (e.g. by smoking) among others (Jacob et al., 1999).

Table 3
Levels of PAHs metabolites in adults' urine samples for all countries participating in the HBM4EU Aligned Studies. Both urinary concentrations (in μg/L) and standardized values (in μg/g creatinine) are presented.

Metabolites	N*	N < LOD	N < LOQ	AM*	GM (95 % CI) *	P5*	P25*	P50*	P75*	P90*	P95*	SD*
Volume-based urinary levels (μg/L)												
1-OHNAP	2611	82	397	4.648	1.25 (1.178–1.327)	0.15	0.43	1.2	3.103	9.258	15.57	0.03
2-OHNAP	2611	6	24	9.497	4.551 (4.337–4.776)	0.53	1.994	4.737	10.918	22.2	32.025	0.11
1,2-DHN	210	1	2	4.742	3.185 (2.835–3.578)	0.848	1.85	3.086	5.331	10.009	14.959	0.448
2-OHFLUO	1750	41	39	0.562	0.288 (0.273–0.303)	0.06	0.14	0.25	0.52	1.378	2.147	0.02
3-OHFLUO	1510	171	300	0.234	0.105 (0.098–0.113)	0.02	0.04	0.087	0.214	0.593	0.995	0.011
9-OHFLUO	411	18	24	0.591	0.401 (0.368–0.437)	0.11	0.233	0.379	0.677	1.141	1.711	0.037
1-OHPHEN	1843	84	42	0.211	0.127 (0.122–0.133)	0.03	0.07	0.12	0.23	0.437	0.648	0.011
2-OHPHEN	1633	3	69	0.13	0.075 (0.072–0.079)	0.019	0.038	0.067	0.132	0.254	0.368	0.007
3-OHPHEN	1843	14	136	0.133	0.081 (0.077–0.084)	0.021	0.041	0.072	0.148	0.277	0.426	0.01
4-OHPHEN	2083	409	200	0.1	0.05 (0.047–0.053)	0.009	0.02	0.05	0.1	0.22	0.352	0.005
9-OHPHEN	1843	600	101	0.263	0.124 (0.116–0.133)	0.02	0.047	0.123	0.3	0.558	0.815	0.006
3-OHBAP	1633	987	464									
1-OHPYR	2371	56	42	0.205	0.109 (0.104–0.114)	0.02	0.05	0.1	0.21	0.462	0.746	0.01
Σ(1-OHNAP and 2-OHNAP)	2611			13.34	5.912 (5.633–6.205)	0.763	2.552	6.054	14.13	29.695	45.169	0.006
Σ(1-OHNAP, 2-OHNAP, and 1,2-DHN)	210			21.197	13.495 (11.869–15.343)	2.849	7.072	13.817	24.103	49.558	65.682	1.078
Σ(2-OHFLUO and 3-OHFLUO)	1510			0.728	0.343 (0.323–0.364)	0.053	0.163	0.3	0.679	1.865	2.901	0.006
Σ(2-OHFLUO, 3-OHFLUO, and 9-OHFLUO)	411			1.359	0.767 (0.69–0.851)	0.115	0.401	0.687	1.534	3.277	4.691	0.04
Σ(1-OHPHEN, 2-OHPHEN, and 4-OHPHEN)	1633			0.385	0.232 (0.222–0.243)	0.054	0.128	0.221	0.408	0.746	1.106	0.009
Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, and 4-OHPHEN)	1633			0.497	0.303 (0.29–0.317)	0.07	0.168	0.29	0.519	0.976	1.401	0.012
Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, and 9-OHPHEN)	1633			0.679	0.401 (0.383–0.419)	0.097	0.203	0.365	0.732	1.389	1.984	0.042
Standardized urinary levels (μg/g creatinine)												
1-OHNAP	2611	82	397	4.469	1.057 (1–1.118)	0.154	0.406	0.892	2.568	6.98	11.44	0.031
2-OHNAP	2611	6	24	7.185	3.989 (3.824–4.161)	0.676	1.851	4.044	8.486	16.012	21.979	0.081
1,2-DHN	210	1	2	2.44	1.804 (1.633–1.992)	0.625	1.099	1.667	2.722	4.857	7.525	0.353
2-OHFLUO	1750	41	39	0.404	0.216 (0.205–0.227)	0.053	0.107	0.177	0.404	0.959	1.553	0.01
3-OHFLUO	1510	171	300	0.172	0.075 (0.07–0.081)	0.013	0.031	0.063	0.169	0.368	0.65	0.006
9-OHFLUO	411	18	24	0.472	0.317 (0.291–0.346)	0.074	0.187	0.318	0.544	0.878	1.163	0.037
1-OHPHEN	1843	84	42	0.178	0.11 (0.105–0.115)	0.024	0.061	0.108	0.193	0.373	0.537	0.005
2-OHPHEN	1633	3	69	0.114	0.067 (0.064–0.07)	0.019	0.035	0.059	0.114	0.216	0.328	0.009
3-OHPHEN	1843	14	136	0.111	0.067 (0.064–0.07)	0.017	0.034	0.063	0.122	0.229	0.361	0.007
4-OHPHEN	2083	409	200	0.087	0.04 (0.038–0.043)	0.009	0.02	0.038	0.074	0.157	0.248	0.002
9-OHPHEN	1843	600	101	0.233	0.115 (0.108–0.122)	0.024	0.051	0.108	0.237	0.442	0.668	0.008
3-OHBAP	1633	987	464									
1-OHPYR	2371	56	42	0.161	0.095 (0.091–0.098)	0.022	0.047	0.087	0.18	0.341	0.515	0.006
Σ(1-OHNAP and 2-OHNAP)	2611			10.947	5.225 (5.007–5.453)	0.934	2.383	5.109	11.272	21.928	31.573	0.002
Σ(1-OHNAP, 2-OHNAP, and 1,2-DHN)	210			10.839	7.809 (7.026–8.68)	2.593	4.262	7.428	13.821	22.451	29.176	1.321
Σ(2-OHFLUO and 3-OHFLUO)	1510			0.538	0.268 (0.253–0.283)	0.059	0.129	0.219	0.539	1.375	2.12	0.001
Σ(2-OHFLUO, 3-OHFLUO, and 9-OHFLUO)	411			1.037	0.617 (0.559–0.681)	0.117	0.329	0.573	1.187	2.349	3.598	0.046
Σ(1-OHPHEN, 2-OHPHEN, and 4-OHPHEN)	1633			0.349	0.213 (0.204–0.222)	0.058	0.118	0.194	0.349	0.671	1	0.003
Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, and 4-OHPHEN)	1633			0.453	0.277 (0.266–0.29)	0.077	0.152	0.253	0.459	0.912	1.372	0.003
Σ(1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, and 9-OHPHEN)	1633			0.621	0.367 (0.351–0.384)	0.099	0.195	0.324	0.632	1.242	1.88	0.012

* (a) the number of samples (N), (b) the arithmetic mean (AM), (c) the geometric mean (GM) with a 95% confidence interval (CI), (d) the 5th percentile (P5), (e) 25th percentile (P25), (f) 50th percentile (P50), (g) 75th percentile (P75), (h) 90th percentile (P90), (i) 95th percentile (P95), (j) standard deviation (SD).

Notably, the strong positive correlation between 3-OHPHEN and 2-OHPHEN (r = 0.94) is due to their shared origin as metabolites of phenanthrene which are produced through the same metabolic pathways involving cytochrome P450 enzymes. Additionally, their similar environmental behavior and analytical detection processes further contribute to their correlated concentrations. Phenanthrene metabolites are highly correlated with fluorene metabolites. These correlations likely arise from their co-occurrence in environmental sources such as combustion emissions (Wang et al., 2003). Their production through similar metabolic pathways and shared environmental exposure patterns further explains the observed relationship. 1-OHPYR was found to be correlated with all phenanthrene's metabolites (1-OHPEN: 0.60; 2-OHPEN: 0.81; 3-OHPEN: 0.85; 4-OHPEN: 0.61; 9-OHPEN: 0.79) which is a result mediated by similar enzymatic pathways (Jacob et al., 1999).

The variability in correlation strength among biomarkers underscores the complexity of PAH metabolism. For instance, while some metabolites of different PAHs exhibit strong correlations, others show less robust relationships, such as between the two naphthalene metabolites (2-OHNAP and 1-OHPHEN, r = 0.29). In case of the metabolite 2-OHNAP there are presumptions on alternative unidentified sources of exposure other than the parent compound (Naphthalene) (Burkhardt et al., 2023). Additional exposure sources for 2-OHNAP (such as dyes or fragrance compounds carrying a 2-OHNAP-moiety) could also explain the low correlation with other PAH metabolites. These alternative sources may help explain the observed low correlation between 2-OHNAP and other PAH metabolites, as they suggest that 2-OHNAP is not solely derived from naphthalene or typical PAH exposure pathways.

To conclude, these correlations between PAH metabolites can help in

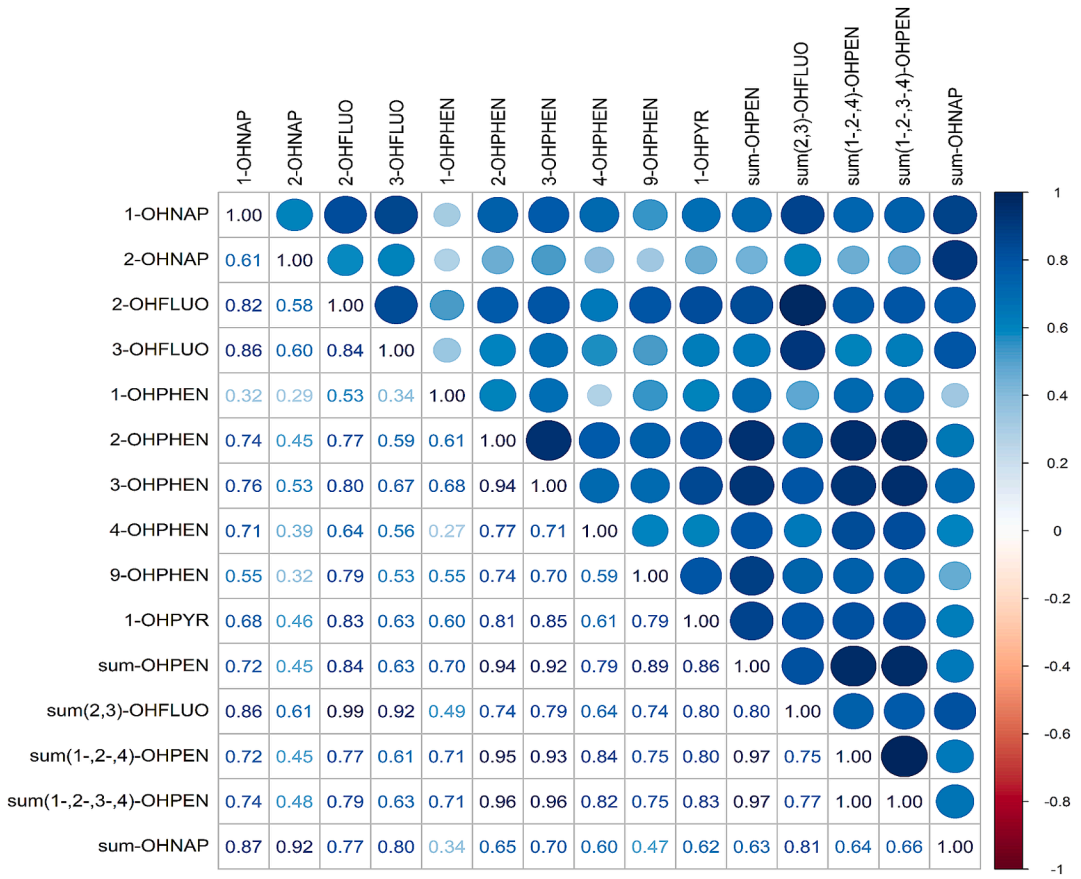

Fig. 1. Pearson correlation matrix between the ln-transformed creatinine standardized exposure biomarkers. The strong positive correlation between 3-OHPHEN and 2-OHPHEN is attributed to their common origin as metabolites of phenanthrene metabolized through cytochrome P450 enzymes. Their similar environmental behaviors and detection methods further reinforce this correlation. Additionally, phenanthrene metabolites are highly correlated with fluorene metabolites due to their concurrent presence in common environmental sources like combustion emissions. The correlation between 1-OHPYR and phenanthrene metabolites (ranging from 0.60 to 0.85) is driven by shared enzymatic pathways (Jacob et al., 1999).

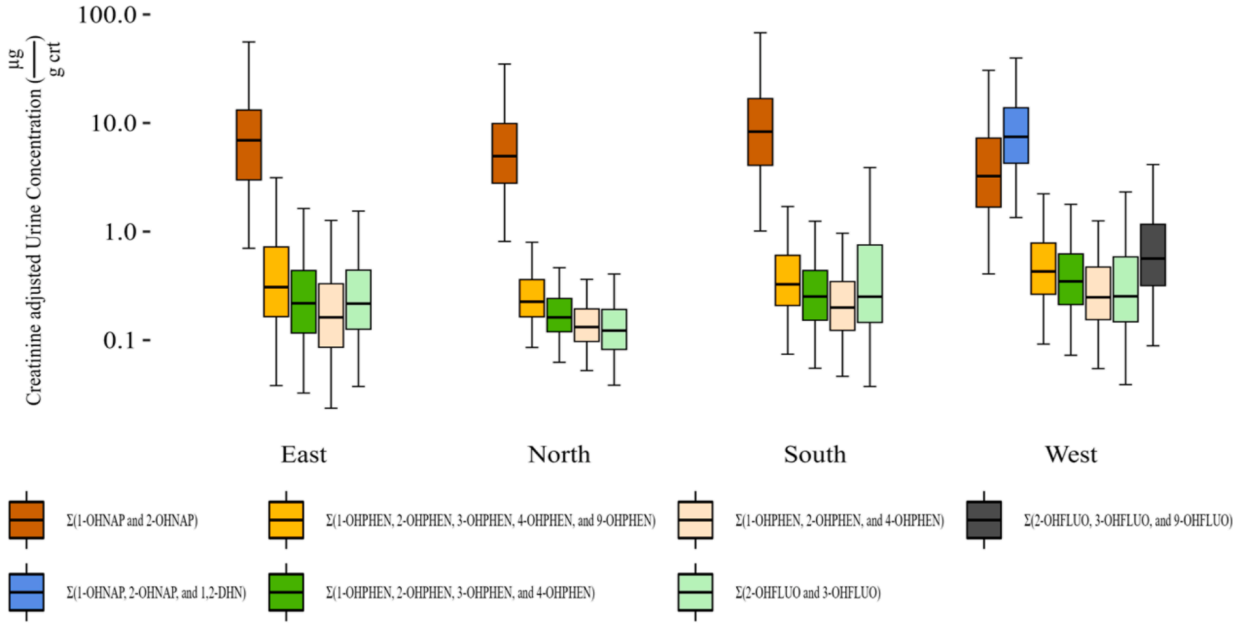

Fig. 2. Geographical distribution of the metabolites' sums (Standardized values; µg/g creatinine). The detection of Σ(1-OHNAP, 2-OHNAP, and 1,2 DHN) is exclusive to Western regions as it was measured solely by Luxembourg. Similarly, Σ(2-OHFLUO, 3-OHFLUO, and 9-OHFLUO) is identified in data from France and Luxembourg, highlighting the limited geographical scope of the measurements.

the identification of shared exposure sources and common metabolic pathways, providing insights into the environmental or occupational origins of contamination which is significantly important for risk assessment and developing targeted strategies to reduce exposures.

3.5. Univariate stratification of urinary PAHs metabolites in multiple levels

Based on the prior knowledge of the research group as well as a univariate analysis conducted (data not shown) four primary variables (gender, smoking status, educational level, and degree of urbanization) were selected beforehand in order to stratify the exposure of European citizens to PAHs. Analysis was conducted at numerous levels, encompassing geographical regions (East, North, South, and West), country-specific evaluations, and considerations based on lifestyle factors such as sex, smoking habits, education levels, and urbanization. Understanding the geographical distribution of PAH biomarkers is essential for elucidating regional differences in exposure patterns and their consequences on public health (Lin et al., 2016, Joksić et al., 2022, Zhang and Li, 2023). For a comprehensive and holistic overview of total exposure, Fig. 2, illustrates the creatinine-standardised sums (μg/g creatinine). Correspondingly, volume-based sums of PAHs in urine (μg/L) are available in the supplementary material (Figure S1). It is apparent that the sum of Σ(1-OHNAP and 2-OHNAP) is notably magnitudes higher compared to other sums, which exhibit comparable magnitudes. Table 4 provides a comprehensive overview of the distribution of PAH biomarkers by geographical location. Similarly, the table with the volume-based levels is included in the supplementary material (Table S6). Fig. 3 shows a heatmap of the GMs of PAH metabolites (creatinine-standardized levels; μg/g creatinine), illustrating regional differences based on country-specific measurements. It is important to note that the intensity of the colors does not indicate risk or toxicity patterns. Moreover, as can be seen from Fig. 3 naphthalene metabolites (1-OHNAP and 2-OHNAP) have been measured universally and due to that fact, their sum is selected to be presented in main text of this study. To this end, an overview of the Σ(1-OHNAP and 2-OHNAP) regarding the exposure of European adults (urine volume-based (μg/L) and creatinine-standardized (μg/g creatinine)) in accordance with their regional level is presented in Fig. 4. The rest are presented in supplementary material (Figures S2-S20). Additionally, we also present the exposure of European citizens to PAHs stratified by sex. The relationship between PAHs exposure and sex remains intricate and partly elusive since various studies yield conflicting findings. While some studies have found no significant difference in PAHs exposure between men and women (Thai et al., 2016, Badlam et al., 2020), others have reported that women are more susceptible to PAH exposure compared to men (Guo et al., 2014, Uppstad et al., 2011). Additionally, exposure to PAHs in women has been associated with detrimental impacts on reproductive health, including premature ovarian failure and imbalances in reproductive hormones (Rafiee et al., 2023). Supplementary materials present detailed statistics on volume-based and creatinine-standardised PAH exposure levels by gender (Tables S7–S9). Fig. 5 and supplementary figures (S21–S57) illustrate gender stratification for specific PAH metabolites and sums, highlighting regional exposure differences (both volume-based and standardised urinary levels are provided). The findings of this study align with existing literature, highlighting the variations in PAH exposure between women and men (Xing et al., 2023, Dobraca et al., 2020, Liu et al., 2021, Zhu et al., 2023, Thai et al., 2020, Hou et al., 2023, Hecht et al., 2006).

Participants were also stratified according to their smoking status. Data on smoking status were collected through self-reported questionnaires, where participants provided information about their smoking habits by answering specific questions. Smoking habit is a key factor in PAHs exposure (Ma and Harrad, 2015). Detailed regional results are provided in the supplementary material (Table S10: volume-based levels and creatinine standardised levels) and more detailed results per country level at Tables S11 and S12 for the volume-based levels and creatinine standardised levels accordingly. Visual representations of the results for all metabolites and their aggregates are presented in Figures S58–S94 (both standardised and volume-based levels). Additionally, Fig. 6 illustrates the total exposure to 1-OHNAP and 2-OHNAP metabolites of non-smokers and smokers. Based on the results of the present study (Fig. 6), it is evident that smokers consistently exhibit higher levels of PAH exposure compared to non-smokers which is something that is supported by other studies as well (Huang et al., 2022, St. Helen et al., 2012, Ratelle et al., 2020, Tabatabaei et al., 2022, Yuan et al., 2011). No effect of smoking on 1-OHNAP and 2-OHNAP excretion was found in the Czech study group, possibly due to other exposure sources. This underscores the potential role of non-smoking-related exposure sources in this population such as environmental pollution, occupational exposure, or specific dietary habits. Furthermore, the participants in the study were stratified according to the ISCED system. Summary statistics at the regional level are provided in Table S13, including both volume-based urine levels and creatinine-standardised values. Country-specific statistics are detailed in Tables S14 and S15. The combined exposure to 1-OHNAP and 2-OHNAP is presented in Fig. 7 (creatinine- standardised values), with additional figures also presented in the supplementary material (Figures S95-S131). Our findings are totally aligned with the work of Suwan-Ampai et al. (2009) in which educational level is inversely associated with PAH exposure.

Exposure to PAHs is also influenced by the degree of urbanization as demonstrated in the study of Palazzi et al. (2019). They observed that children residing in Paris (urban or suburban areas, comparable to the classifications in our study) exhibited higher exposure levels compared to those living on Yeu Island (a rural area). This finding aligns closely with our results across all countries, except for Denmark, as illustrated in Figures S95–S131 in which stratify participants solely based on their urbanization level and the data has not been normalized yet as will be done in the multivariate analysis following in the next section. The supplementary material includes comprehensive urbanization-based stratification of PAH exposure across cities, towns or suburbs, and rural areas. Table S16 details regional PAH urine levels, with country-specific results in Tables S17 and S18. Illustrative figures (S132-S168) and Fig. 8 present Σ(1-OHNAP and 2-OHNAP) levels by urbanization.

3.6. Multivariate linear regression modelling

The multivariate linear regression analysis yielded significant results regarding the determinants of exposure for each PAH metabolite. Detailed results for each metabolite are provided in the Supplementary Material (Tables S19–S23). All models demonstrated a high statistical significance with p-values of < 0.001 and R^2 values exceeding 0.80 except for 1-OHNAP. A summary of each model, along with the independent (influential) variables, is presented qualitatively in Fig. 9. Each metabolite is represented by a unique color, which is associated with all the exposure determinants identified through the multivariate regression analysis. As a result of that, by examining the colors associated with each determinant of exposure, it is possible to identify the parameters linked to each metabolite. A clearer view regarding the determinants of exposure for each parent compound is also presented in Figs. 10–13. Last but not least, it is important to mention that for illustration purposes the sample type (morning urine, 24 h urine, urine spot) has been removed from plots.

For the naphthalene metabolites (Fig. 10), specifically, 1-OHNAP was found to have a statistically significant association with smoking status (active or passive) and the number of cigarettes smoked within a 24-hour period. Nevertheless, both active and passive smoking showed a negative contribution whereas the number of cigarettes smoked daily had a positive contribution. To this end the low Variance Inflation Factor (VIF < 5) with the high statistical significance might be an indication for a dose–response relationship between 1-OHNAP and the number of cigarettes smoked daily. The type of sample selected also appears to

Table 4
Geographic comparison for pahs biomarkers, urinary levels standardised for creatinine (μg/g creatinine).

Metabolites (N)	Statistical test	North vs South	North vs East	North vs West	South vs East	West vs East	South vs West
		*N_{total}: 1039	*N_{total}: 971	*N_{total}: 1487	*N_{total}: 1124	*N_{total}: 1572	*N_{total}: 1640
	Standardised urinary levels (μg/g creatinine)						
1-OHNAP	**Effect Size: Cohen's d**	0.125	0.093	0.013	0.034	0.006	0.009
	p-value	<0.001	0.002	0.431	0.271	0.733	0.614
	GM (95 % CI)	1.208 (1.108–1.317)	1.307 (1.21–1.413)	0.526 (0.488–0.567)	1.365 (1.25–1.491)	0.600 (0.555–0.650)	0.59 (0.544–0.639)
	P95 (95 % CI)	10.455 (8.773–12.015)	11.169 (9.262–13.487)	6.607 (5.545–7.765)	13.182 (11.442–14.032)	9.008 (7.848–11.677)	8.700 (7.664–10.435)
2-OHNAP	**Effect Size: Cohen's d**	0.13	0.045	0.059	0.089	0.111	0.204
	p-value	<0.001	0.163	0.034	0.003	<0.001	<0.001
	GM (95 % CI)	5.06 (4.75–5.39)	4.209 (3.937–4.499)	3.158 (2.990–3.336)	5.257 (4.93–5.605)	3.329 (3.148–3.521)	3.778 (3.574–3.994)
	P95 (95 % CI)	26.91 (22.37–31.74)	20.587 (18.477–24.404)	17.89 (15.864–20.115)	26.918 (24.361–30.304)	20.307 (18.343–21.36)	22.574 (20.993–25.786)
2-OHFLUO	**Effect Size: Cohen's d**	0.24	0.126	0.168	0.013	0.032	0.072
	p-value	<0.001	0.004	<0.001	0.746	0.443	0.022
	GM (95 % CI)	0.205 (0.193–0.218)	0.166 (0.157–0.177)	0.169 (0.160–0.178)	0.244 (0.229–0.26)	0.202 (0.191–0.213)	0.237 (0.224–0.25)
	P95 (95 % CI)	1.51 (1.32–1.74)	0.990 (0.855–1.204)	1.271 (1.002–1.462)	1.766 (1.504–1.958)	1.492 (1.202–1.72)	1.706 (1.542–1.826)
3-OHFLUO	**Effect Size: Cohen's d**	0.144	0.099	0.227	0.028	0.101	0.178
	p-value	<0.001	0.008	<0.001	0.511	0.008	<0.001
	GM (95 % CI)	0.034 (0.032–0.037)	0.029 (0.027–0.032)	0.052 (0.049–0.056)	0.038 (0.035–0.041)	0.056 (0.052–0.06)	0.052 (0.049–0.056)
	P95 (95 % CI)	0.354 (0.301–0.403)	0.314 (0.228–0.408)	0.722 (0.556–0.968)	0.379 (0.324–0.45)	0.744 (0.603–0.968)	0.613 (0.49–0.71)
1-OHPHEN	**Effect Size: Cohen's d**	0.162	0.037	0.177	0.182	0.202	0.031
	p-value	<0.001	0.353	<0.001	<0.001	<0.001	0.250
	GM (95 % CI)	0.108 (0.103–0.114)	0.036 (0.033–0.039)	0.12 (0.114–0.125)	0.069 (0.063–0.074)	0.08 (0.075–0.086)	0.13 (0.124–0.136)
	P95 (95 % CI)	0.513 (0.425–0.619)	0.218 (0.182–0.248)	0.522 (0.462–0.57)	0.503 (0.408–0.604)	0.512 (0.454–0.569)	0.568 (0.512–0.611)
2-OHPHEN	**Effect Size: Cohen's d**	0.148	0.147	0.182	0.097	0.121	0.045
	p-value	<0.001	<0.001	<0.001	0.027	0.007	0.122
	GM (95 % CI)	0.054 (0.051–0.057)	0.065 (0.061–0.069)	0.06 (0.058–0.063)	0.066 (0.062–0.07)	0.073 (0.07–0.076)	0.062 (0.06–0.065)
	P95 (95 % CI)	0.312 (0.259–0.431)	0.328 (0.239–0.528)	0.234 (0.204–0.263)	0.434 (0.335–0.546)	0.316 (0.261–0.379)	0.311 (0.273–0.366)
3-OHPHEN	**Effect Size: Cohen's d**	0.16	0.138	0.302	0.058	0.015	0.131
	p-value	<0.001	<0.001	<0.001	0.172	0.727	<0.001
	GM (95 % CI)	0.041 (0.039–0.044)	0.045 (0.042–0.047)	0.073 (0.069–0.076)	0.048 (0.045–0.052)	0.079 (0.075–0.082)	0.066 (0.063–0.07)
	P95 (95 % CI)	0.302 (0.236–0.373)	0.219 (0.165–0.342)	0.329 (0.293–0.372)	0.37 (0.281–0.421)	0.359 (0.311–0.411)	0.361 (0.326–0.403)
4-OHPHEN	**Effect Size: Cohen's d**	0.029	0.148	0.066	0.139	0.138	0.024
	p-value	0.312	<0.001	0.017	0.002	0.003	0.405
	GM (95 % CI)	0.025 (0.024–0.027)	0.029 (0.026–0.031)	0.027 (0.026–0.029)	0.029 (0.027–0.032)	0.031 (0.029–0.033)	0.028 (0.026–0.029)
	P95 (95 % CI)	0.147 (0.119–0.172)	0.245 (0.195–0.301)	0.176 (0.155–0.206)	0.245 (0.199–0.296)	0.26 (0.23–0.304)	0.185 (0.155–0.217)
9-OHPHEN	**Effect Size: Cohen's d**	0.081	0.125	0.028	0.078	0.145	0.088

(*continued on next page*)

Table 4 (*continued*)

Metabolites (N)	Statistical test	North vs South	North vs East	North vs West	South vs East	West vs East	South vs West
		*N_{total}: 1039	*N_{total}: 971	*N_{total}: 1487	*N_{total}: 1124	*N_{total}: 1572	*N_{total}: 1640
	Standardised urinary levels (μg/g creatinine)						
	p-value	<0.001	<0.001	0.253	0.058	0.002	0.003
	GM (95 % CI)	0.08 (0.075–0.085)	0.085 (0.079–0.092)	0.067 (0.064–0.070)	0.088 (0.083–0.095)	0.074 (0.07–0.079)	0.074 (0.07–0.077)
	P95 (95 % CI)	0.546 (0.454–0.627)	0.645 (0.475–0.85)	0.364 (0.332–0.423)	0.641 (0.558–0.798)	0.499 (0.427–0.626)	0.486 (0.417–0.574)
3-OHBAP	**Effect Size: Cohen's d**	0.293	0.216	0.644	0.400	0.981	0.578
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	GM (95 % CI)	0.055 (0.051–0.059)	0.024 (0.023–0.025)	0.0001 (0.0–0.001)	0.046 (0.043–0.05)	0.001 (0.001–0.001)	0.003 (0.003–0.004)
	P95 (95 % CI)	0.384 (0.348–0.431)	0.088 (0.072–0.12)	0.051 (0.041–0.07)	0.371 (0.333–0.41)	0.039 (0.032–0.044)	0.338 (0.311–0.371)
1-OHPYR	**Effect Size: Cohen's d**	0.225	0.225	0.251	0.165	0.136	0.071
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.005
	GM (95 % CI)	0.06 (0.057–0.064)	0.083 (0.077–0.089)	0.084 (0.08–0.088)	0.091 (0.086–0.098)	0.105 (0.1–0.111)	0.089 (0.085–0.094)
	P95 (95 % CI)	0.325 (0.273–0.41)	0.643 (0.525–0.743)	0.409 (0.375–0.461)	0.623 (0.524–0.696)	0.557 (0.485–0.609)	0.435 (0.404–0.486)

* N represents the total number of participants of each subset. ** Effect size =< 0.2: small effect, 0.2 < Effect size =< 0.8: Medium effect, and Effect size > 0.8: Large effect.

Metabolites	ALL	North		East		South		West			
		Iceland	Denmark	Poland	Czech Republic	Croatia	Portugal	France	Germany	Switzerland	Luxemburg
1-OHNAP	0.793	0.846	1.440	2.589	0.966	1.676	0.961	1.110	0.383	0.137	0.582
2-OHNAP	3.933	2.955	5.025	7.909	2.872	4.975	7.489	6.097	1.325	2.878	4.778
1,2-DHN	1.773										1.773
2-OHFLUO	0.204	0.114	0.177		0.205	0.242	0.293	0.361			0.113
3-OHFLUO	0.043	0.023			0.035	0.038	0.041	0.128			0.050
9-OHFLUO	0.251							0.432			0.149
1-OHPHEN	0.091	0.075			0.022	0.104	0.146	0.189	0.152		0.083
2-OHPHEN	0.063	0.044			0.084	0.038	0.089	0.089	0.057		
3-OHPHEN	0.060	0.032			0.056	0.024	0.086	0.129	0.080		0.078
4-OHPHEN	0.028	0.017	0.033		0.036	0.026	0.027	0.027	0.023		0.045
9-OHPHEN	0.077	0.069			0.099	0.068	0.103	0.062	0.082		0.050
1-OHPYR	0.087	0.033		0.268	0.062	0.050	0.109	0.132	0.067	0.079	0.207
3-OHBAP	0.006	0.028			0.021	0.021	0.225	0.000	0.000		

Fig. 3. Geometric means comparison of PAH metabolites between the countries and European regions (creatinine-standardized urinary levels in μg/g creatinine). In the present table we provide a heatmap-overview of the geometric means depending on the measurements that each country performed in relation to the rest of the countries for each metabolite. The lowest value for each metabolite is zero. In the heatmap, lower values are represented by green shades, transitioning to red for higher values. The intensity of the color does not reflect a risk or toxicity pattern but is intended solely for comparison purposes, highlighting the need for a more in-depth analysis to derive meaningful conclusions about potential risks or toxicity associated with these levels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

influence negatively the measured levels of 1-OHNAP. A similar pattern was observed in the analysis of 2-OHNAP, where, in addition to cigarette smoke exposure, a statistically significant correlation was found with the season during which the sample was collected. While the sampling season was also found to influence the exposure patterns of 1-OHNAP (winter and spring identified with higher exposure levels compared to the other seasons), this effect was not statistically significant. Notably, for both metabolites and cigarette smoke exposure, the VIF was less than five. Similar findings for smoking have been reported by Raponi et al. (2017) and Wang et al. (2024). Dietary habits were also found to contribute to naphthalene exposure, significantly for 1-OHNAP and also for 2-OHNAP. Exposure to open fireplaces was statistically significant for both 1-OHNAP and 2-OHNAP. In the 1-OHNAP model (VIF < 5), winter was set as the reference category, whereas in the 2-OHNAP model (VIF > 5), higher multicollinearity led to the retention of coefficients for all seasons. To this end, the 2-OHNAP model exhibited lower multicollinearity, allowing for the inclusion of coefficients for all seasonal categories. Additionally, 1,2-DHN, which was measured exclusively in Luxembourg, further confirmed the negative contribution of any form of cigarette smoke to exposure levels, except for the mean number of cigarettes smoked on a daily basis which further supports the quantitative relationship of smoking and exposure to naphthalene metabolites. Smoking was also identified as an exposure determinant by Klotz et al. (2011). Degree of urbanization and household income were also found to contribute to 1,2-DHN levels. The levels of PAH exposure were observed to be lower among participants living in more decentralized or rural areas. Finally, the gender of the participants emerged as a determinant of exposure, as it was included in all three models (with p-values < 0.05 in the models for 2-OHNAP and 1,2-DHN). At 1,2-DHN model, seasonal variations were not found to contribute to the exposure levels. It is worth noting that at country level, for instance, in Denmark rural seems to be associated with more PAH exposure than cities/town, which might be unexpected as less exhaustion from traffic is expected in rural areas. However, in Denmark it is more likely to use burning stoves as an

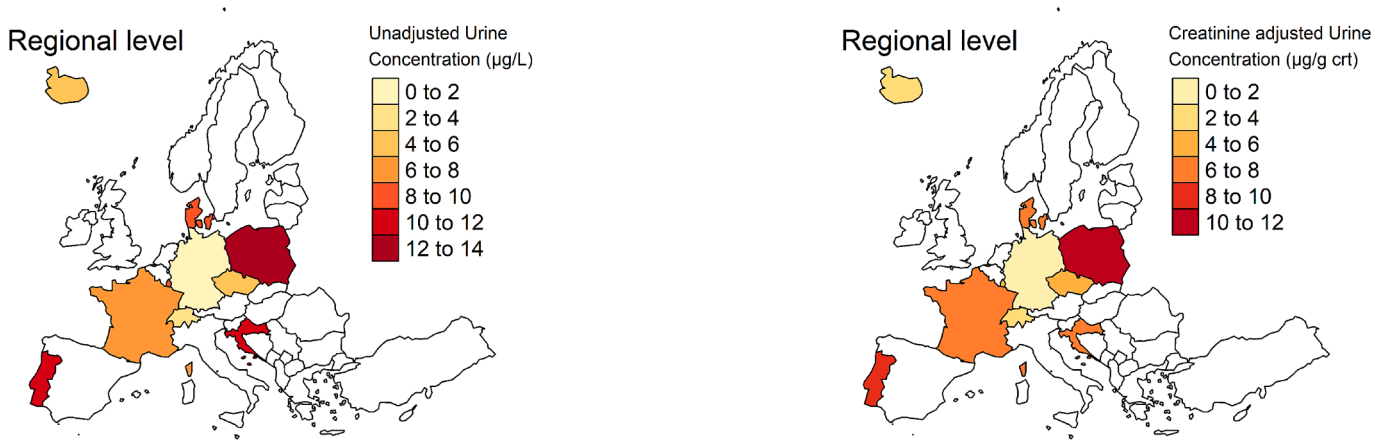

Fig. 4. Geometric means (GM) for Σ(1-OHNAP and 2-OHNAP) in urine unadjusted (µg/L; left) standardized (µg/g creatinine; right) per Regional, NUTS1 and NUTS2 areas. GMs are given only for those areas with 10 or more participants.

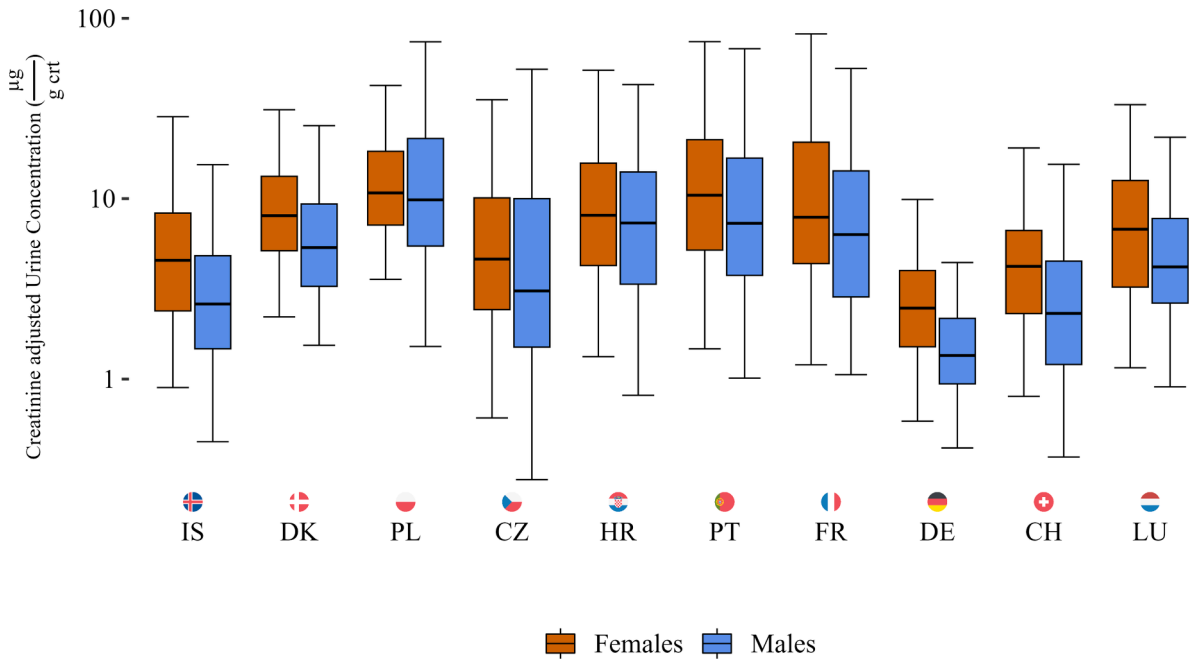

Fig. 5. Creatinine-standardized concentration of Σ(1-OHNAP and 2-OHNAP) in urine (µg/g creatinine) stratified by sex among European citizens. Results have not been adjusted for other influencing factors.

additional source of heating if a participant lives in rural areas compared to cities (data not shown). Gender differences were similarly noted in other studies (Guo et al., 2014, Uppstad et al., 2011, Kim and Karthikraj, 2021) driving the exposure levels in higher levels in females compared to males.

In the models developed for fluorene metabolites (Fig. 11), exposure to cigarette smoke was also found to be statistically significant though with a negative contribution. Nevertheless, the number of cigarettes smoked daily positively correlated with fluorene metabolite levels, further supporting the indication of a dose–response relationship. This indication is reinforced by the low VIFs (<5) and the statistical significance of the associations (<0.05). Wang et al. (2024) also report that some of the fluorene metabolites are related to smoking. It is important to also note that for cigarette-related variables, the VIFs were less than 5 for all the metabolites in question. Furthermore, the sampling season appears to influence exposure levels for all fluorene metabolites. Similar reports are also reported from other studies (Cong et al., 2010, Eiguren-Fernandez et al., 2007, Styszko et al., 2016, Dat et al., 2018). Specifically, for 3-OHFLUO and 9-OHFLUO, the year of sampling was negatively associated with the measured levels. This aspect could indeed be relevant to the REACH regulations, though a time-series analysis would be necessary to confirm any regulatory alignment or patterns over time. Similar evidence was also reported by Li et al. (2021). Our analysis indicates an inverse association between educational levels and exposure levels to 3-OHFLUO, with higher education correlating with reduced exposure.

For all phenanthrene metabolites (Fig. 12), tobacco products were also found to contribute to exposure with statistical significance (smoking and/or passive smoking). For some of them metabolites, tobacco exposure exhibited varying associations. While the number of cigarettes smoked daily showed a positive correlation with most metabolites (except 2-OHPHEN), certain smoking-related variables had negative regression coefficients. Although exposure to smoke is a well-established determinant of PAH exposure, the low number of participants reporting smoking may have contributed to potential statistical bias or false-positive indications. However, in the case of phenanthrene

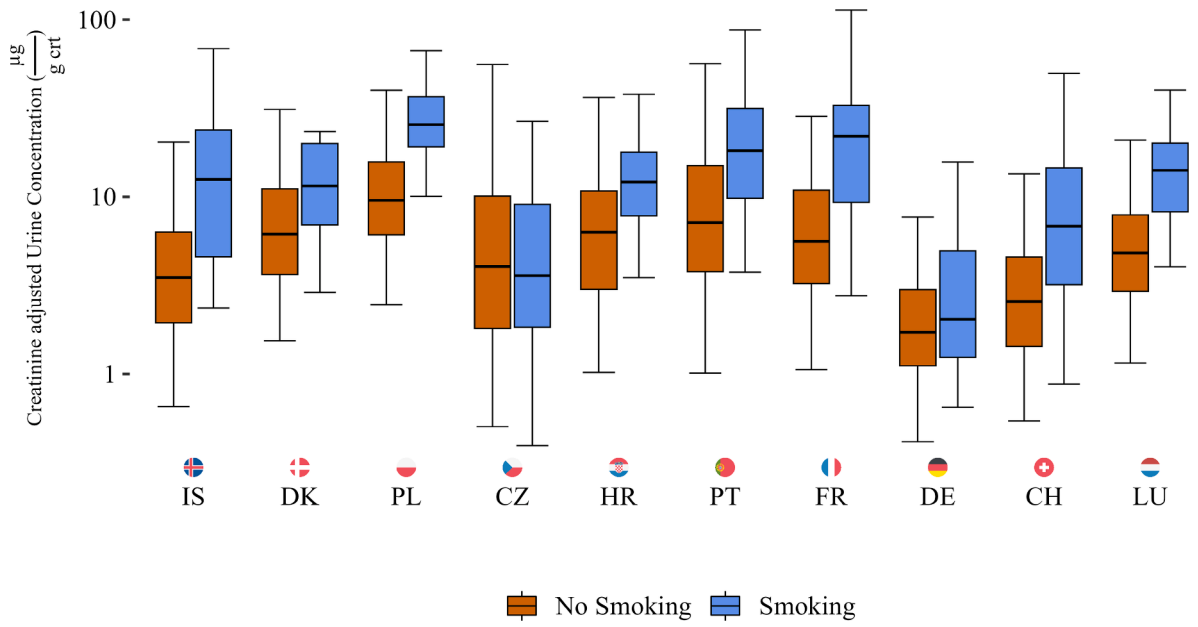

Fig. 6. Creatinine- standardized concentration of Σ(1-OHNAP and 2-OHNAP) in urine (µg/g creatinine) stratified by smoking status among European citizens. Results have not been adjusted for other influencing factors.

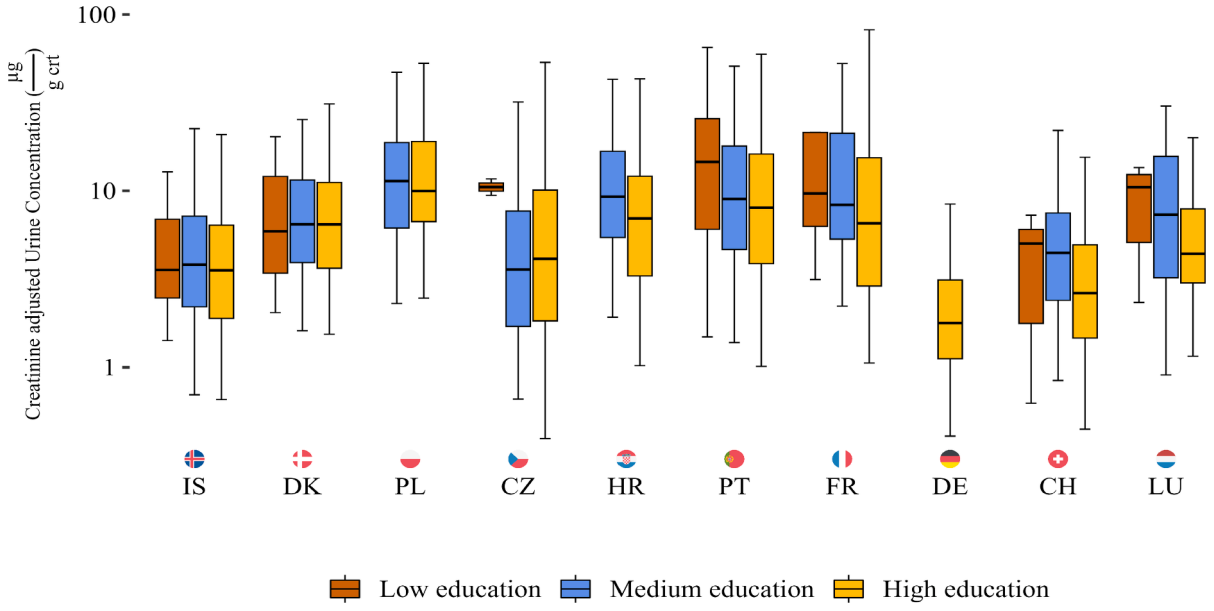

Fig. 7. Creatinine-adjusted concentration of Σ(1-OHNAP and 2-OHNAP) in urine (µg/g creatinine) stratified by educational level among European citizens. Results have not been adjusted for other influencing factors.

metabolites, a strong positive contribution of the number of cigarettes smoked daily was also observed (VIFs < 5; $p < 0.05$), further supporting a dose–response relationship between PAHs and tobacco products. Findings from other studies also confirm our claim about the smoking association and tobacco (Luo et al., 2021; Jacob et al., 1999; Patel et al., 2016). The type of sample (urine-spot, urine-24 h, or morning urine) was statistically significant for nearly all metabolites, with the exception of 2-OHPHEN. The year of sampling was a significant factor for all metabolites except 1-OHPEN and 4-OHPEN contributing both positively and negatively to the exposure levels. Time trends were also reported as contributors to phenanthrene exposure in other studies (Rombolà et al., 2019; Burkhardt et al., 2023). Lastly, gender was found to influence exposure levels for most metabolites, excluding 2-OHPEN and 3-OHPEN. Gender, and more specifically females, were found to be a determinant of exposure in other studies for phenanthrene as well (Hou et al., 2023; Hecht et al., 2006; Guo et al., 2014; Uppstad et al., 2011; Kim and Karthikraj, 2021). The degree of urbanization was also found to contribute inversely to the exposure levels through the 3-OHPHEN metabolite.

For pyrene (Fig. 13), both gender and smoking in any form were found to contribute significantly to pyrene exposure, with females exhibiting higher exposure levels than males. These findings align with previous studies (Suwan-Ampai et al., 2009; Campo et al., 2018), which also identified gender and smoking habits as significant factors influencing pyrene exposure. In the case of 1-OHPYR, the number of cigarettes smoked daily was identified as a positive quantitative contributor to exposure levels. Additionally, passive smoking within 24 h prior to sample collection was also found to positively contribute to increased

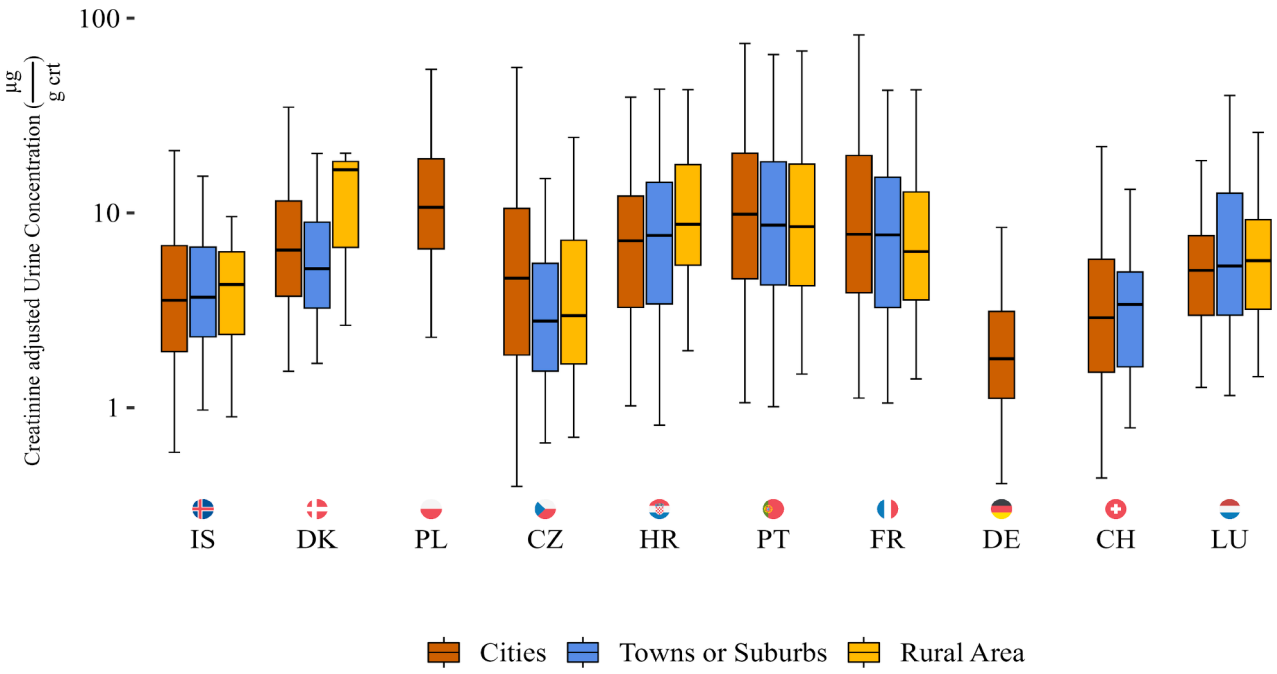

Fig. 8. Creatinine-adjusted concentration of Σ(1-OHNAP and 2-OHNAP) in urine (µg/g creatinine) stratified by degree of urbanization among European citizens. Results have not been adjusted for other influencing factors.

exposure levels. Additionally, the year of sample collection was found to be statistically significant for the levels of 1-OHPYR. The more recently the sample collected the lower levels identified.

One notable point of interest pertains to participants following a vegetarian diet. Traditionally, such diets contain few grilled foods or foods exposed to charcoal. As confirmed by the developed models, very few metabolites showed a correlation with this dietary pattern, and none were statistically significant. Notably, the consumption of local foods or cheeses was found to contribute to exposure levels in nearly all models. However, further research is needed to ascertain whether the consumption of these foods is genuinely associated with exposure levels. Additionally, BMI and weight of participants appeared to be a significant factor influencing exposure, as it was identified in nearly all models; however, it was never associated with a VIF < 5.

It is important to note that the linearity assumption was upheld in all models, and there was no evidence of effect modification, as no significant interactions were observed between exposures and covariates, or between any pair of exposures (data not shown). Overall, the variables selected for stratification were found to contribute significantly to nearly all multivariate linear regression models developed in the context of this study. Last but not least, the relatively small number of smokers in our study likely reduced the statistical power, making it more challenging to detect significant positive associations between most smoking-related categorical variables and PAH exposure levels while a strong positive contribution was identified with the quantitative ones (number of cigarettes smoked daily). To this end, in future PAH studies, more balanced recruitment between individuals with both exposure patterns might provide clearer indications in this direction.

Finally, understanding the determinants of exposure is critically important for advancing the chemical strategy for sustainability. This knowledge facilitates the design and implementation of safer and more sustainable chemicals by design. Identifying key factors influencing human exposure can inform chemical regulation and policymaking, supporting targeted measures such as reducing harmful emissions (e.g., the regulation of specific PAHs under the umbrella of REACH), optimizing product formulations, and promoting sustainable alternatives. Additionally, integrating exposure determinants into decision-making processes aligns with the principles of green chemistry and the circular economy, promoting innovation while safeguarding the protection of human health.

4. Strengths and limitations

One significant advantage of this study is its pioneering nature in evaluating PAH exposure on a European scale, specifically targeting individuals of reproductive age. The inclusion of participants from 10 European countries facilitated the examination of geographic disparities and the identification of factors associated with PAH exposure. Furthermore, the study assessed the potential for PAH exposure based on numerous factors such as geographic region, sex, smoking habits, degree of urbanization, and educational level. Moreover, the extensive dataset includes details on a high number of PAH biomarkers, serving as a foundation for further assessment and statistical linkage between exposure and PAH metabolite urine concentrations, despite potential uncertainties in self-reported data. This research study has numerous constraints. Originally, individual studies were not designed to evaluate only PAH exposure. Consequently, certain PAH-specific questionnaire data, such as consumption of grilled or smoked food, indoor use of biomass, or potential exposure incidents within 48 h before sampling (such as BBQ activities, smoking, or wildfire smoke), are not included in all countries considered. As a result of that limited datasets were introduced in order to assess PAH exposure due to those factors. For example, food patterns were not included in the questionnaires provided in Denmark. In general terms, reporting of dietary habits was limited across all countries, with the exception of participants from Croatia and Switzerland. Additionally, the questionnaires distributed to participants varied by country, resulting in unanswered questions in some cases. Another significant limitation is the reliance on self-reported smoking status without distinguishing former smokers among participants. This leads to an uneven comparison between smokers and non-smokers. Furthermore, a noteworthy observation is the much larger number of non-smokers compared to smokers among the participants leading to misinterpretations regarding smoking status and PAH-related exposure. Additionally, the frequency of exposure to second-hand smoke was not included in all countries' questionnaires resulting in a smaller dataset for the subset tested. The recruitment of participants varied across

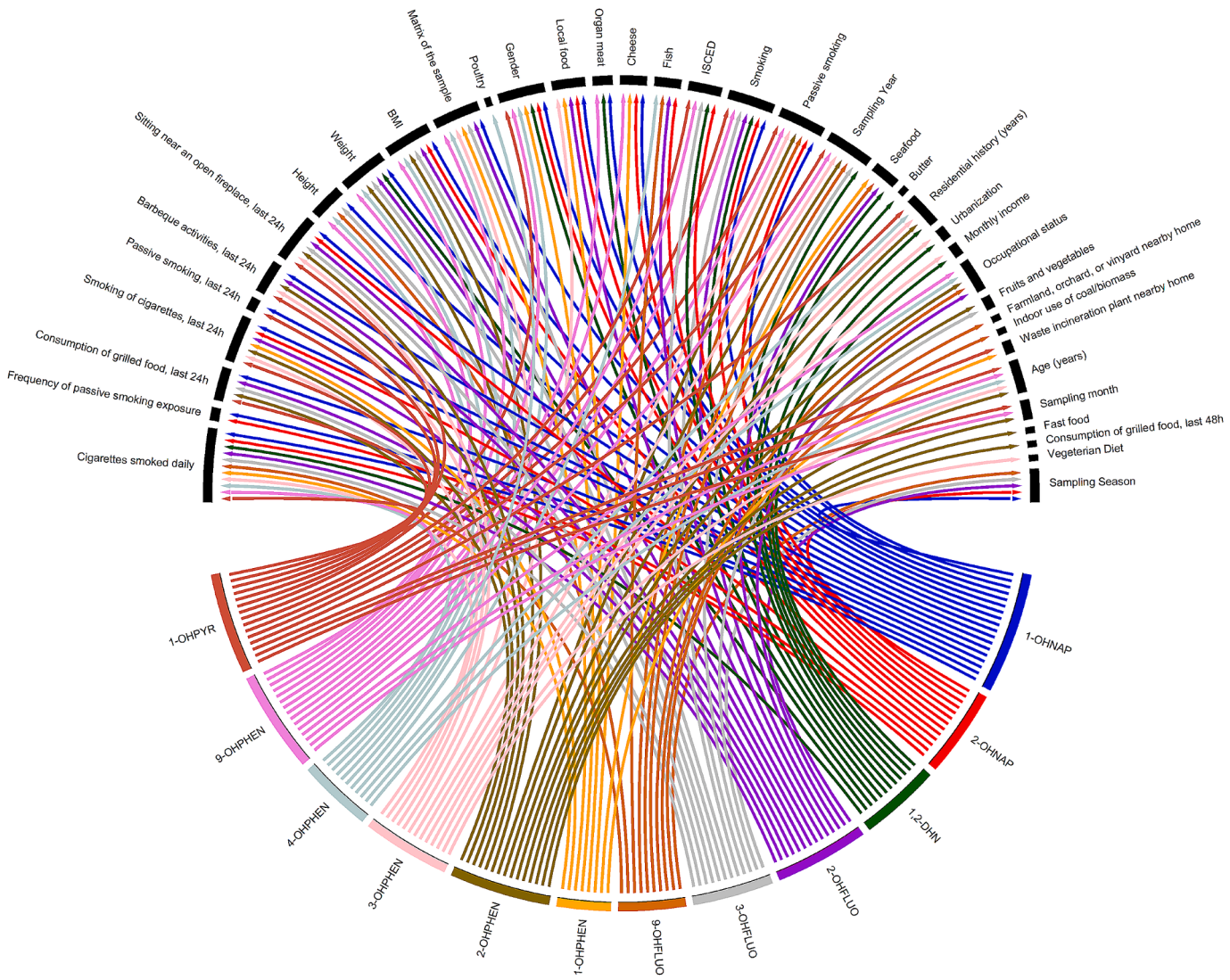

Fig. 9. Variables that are included in each multivariate linear regression model, with each model represented by distinct arrow colors. Each segment along the outer edge represents a variable or biomarker, with lines (chords) connecting variables based on the regression model. The color of the lines corresponds to each one of the metabolites. Variables include smoking behaviors, dietary patterns, residential history, and socioeconomic factors seem to be common among the models developed indicating determinants of exposure to PAHs.

seasons and months, potentially leading to biases arising from differences in exposure events as illustrated by the multivariate linear regression analysis conducted previously. Additionally, the limitations of the study extend to not measuring the same number of metabolites in all countries and variations in urine sample collection methods (urine spot, urine-24 h, and first-morning urine) which was found to be a significant contributor to the exposure levels. While detection limits for most participating countries were comparable, the wider range observed for biomarkers such as 1-OHNAP and 2-OHNAP is primarily due to higher LOQs reported by Poland. Such variability in detection limits may introduce some bias into the results, especially for samples with concentrations near the LOQs. Recognizing this, the European HBM program aims to harmonize analytical methodologies and ensure consistent quality assurance across laboratories to minimize such biases and improve data comparability. One notable limitation that should also be considered pertains to the challenges inherent in inter-country and inter-EU area (North-South-East-West) comparisons. While the studies included were ostensibly regionally and nationally representative, it is recognized that achieving true representativeness in exposure-related research is unattainable. Often, significant variations are observed between different regions within countries, surpassing disparities observed between distinct nations. Furthermore, it is important to acknowledge that some of the studies amalgamated from individual studies and incorporated into the HBM4EU database may not accurately reflect the representativeness of their respective original studies. Consequently, the pursuit of national representativeness becomes further obscured. In summary, while the associations and disparities identified in this study, such as those related to gender, smoking habits, and educational attainment, remain highly pertinent, it is imperative to exercise caution when interpreting geographical disparities and conducting inter-country comparisons. These nuances underscore the complexity of the geographic dimension in the present analysis.

5. Conclusions

In the HBM4EU Aligned Studies, thirteen PAH metabolites (1-OHNAP, 2-OHNAP, 1,2-DHN, 2-OHFLUO, 3-OHFLUO, 9-OHFLUO, 1-OHPHEN, 2-OHPHEN, 3-OHPHEN, 4-OHPHEN, 9-OHPHEN, 1-OHPYR, and 3-OHBAP) were analyzed in the urine samples of adults aged 20–39 from various European regions between 2014–2021, capturing a total of approximately 2611 participants. The study provides detailed exposure metrics. These metrics offer a comprehensive overview for

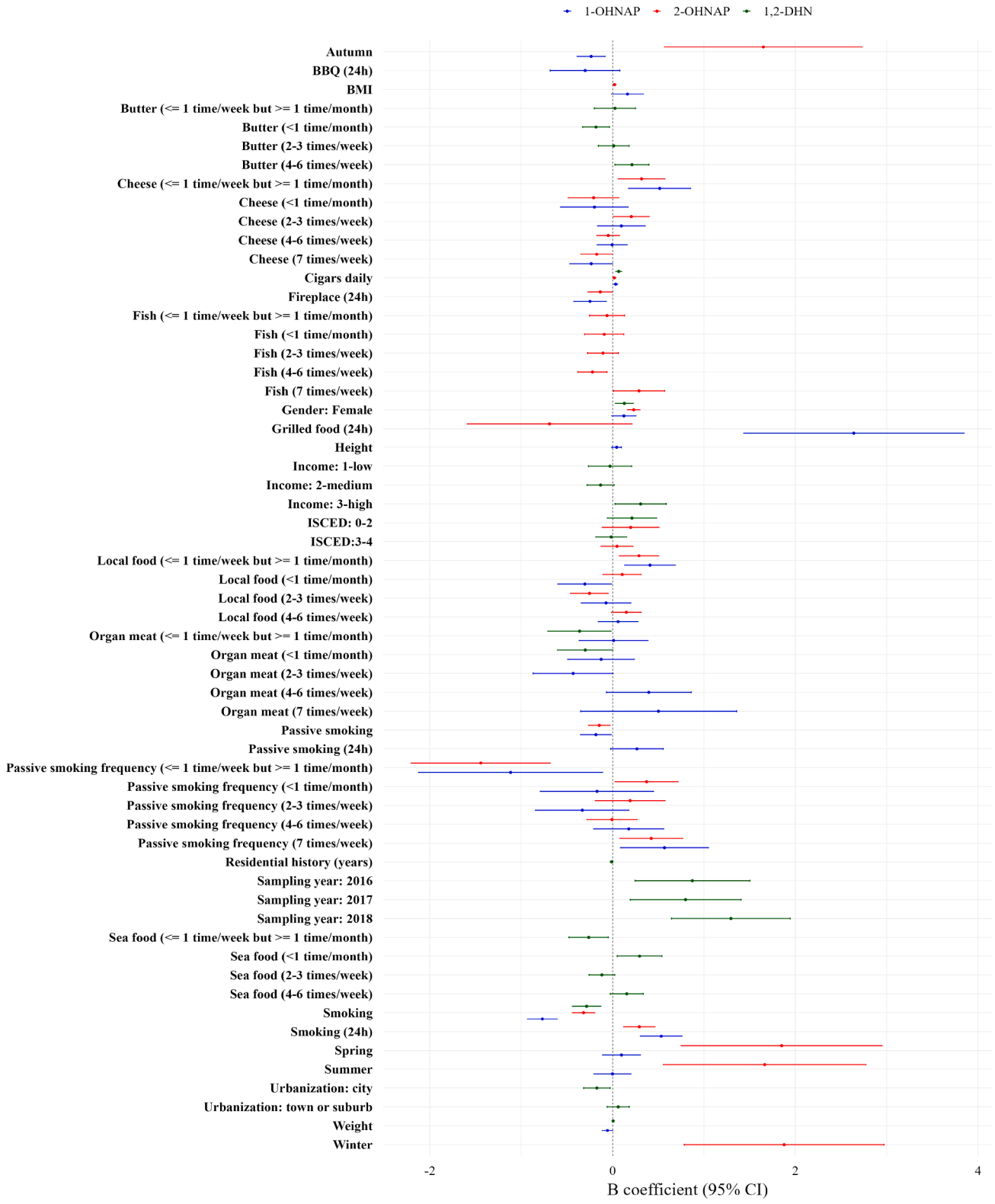

Fig. 10. Naphthalene metabolites. Association of 1-OHNAP and 2-OHNAP levels with cigarette smoke exposure (active and passive), number of cigarettes smoked, sample type, and additional determinants. Measured 1-OHNAP levels were significantly influenced by smoking status and cigarette consumption within 24 h, while sample type negatively affected its levels. Seasonal effects were observed for 1-OHNAP (higher in winter and spring) but were not statistically significant. In contrast, 2-OHNAP showed a significant seasonal correlation alongside smoking exposure. Additional exposure determinants included dietary habits, open fireplace use, urbanization level, household income, and participant gender. It is important to note that in the 1-OHNAP model (VIF < 5), Winter was set as the reference category due to lower multicollinearity, whereas in the 2-OHNAP model (VIF > 5), higher multicollinearity led to the retention of coefficients for all seasons. Notably, 1,2-DHN, measured exclusively in Luxembourg, confirmed significant associations with cigarette smoke exposure. Gender differences in exposure were statistically significant, with higher levels noted among females. For clarity and illustrative purposes, the sample matrix has been omitted from this figure. However, the complete details of this model are provided in Table S19 within the supplementary material for reference.

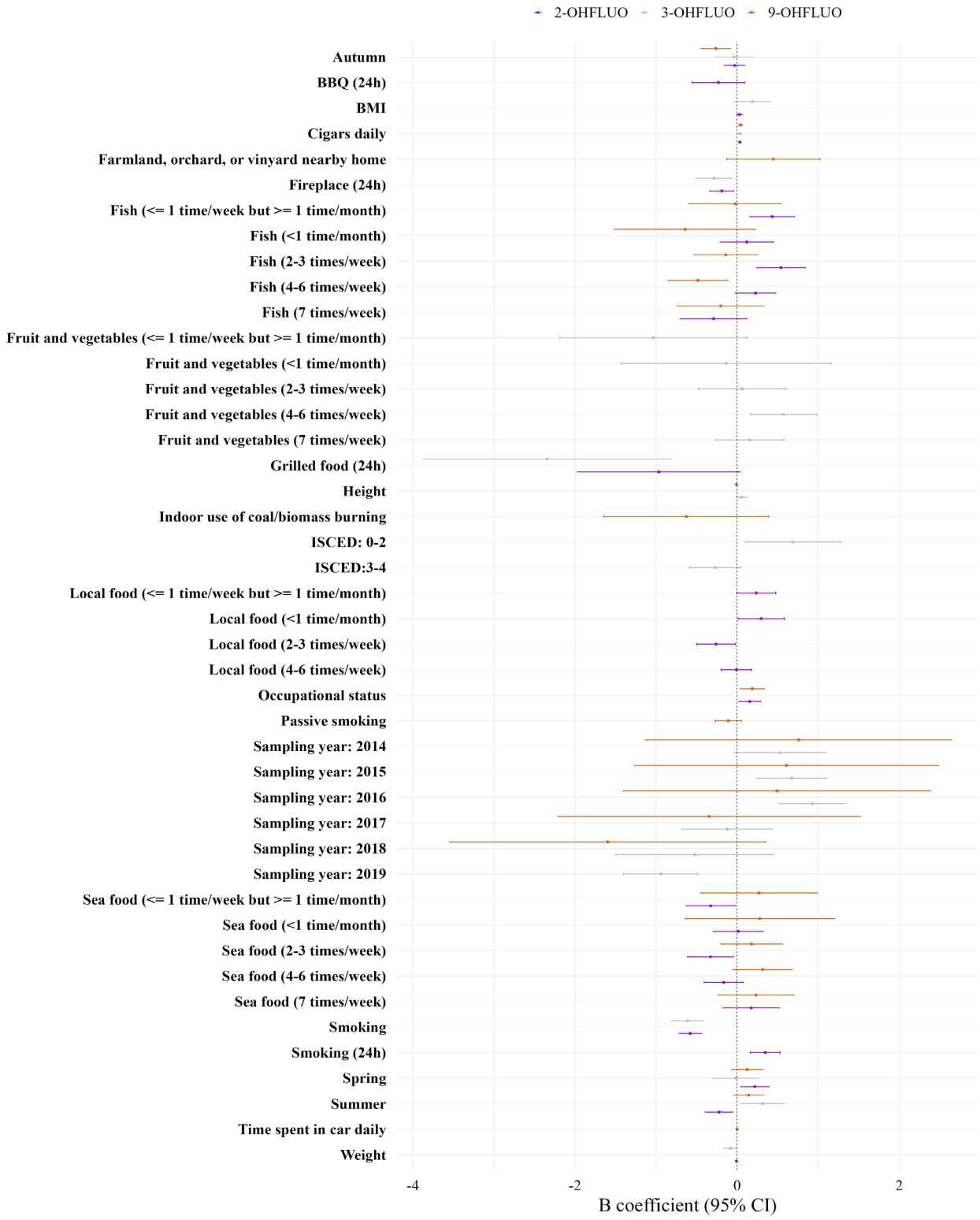

Fig. 11. Fluorene metabolites. Exposure determinants for fluorene metabolites, highlighting the statistically significant role of cigarette smoke exposure. Significant contributors to 2-OHFLUO and 3-OHFLUO exposure included open fire sources (e.g., fireplaces) and consumption of smoked foods within 24 h before sampling. Seasonal variations influenced all fluorene metabolites. Negative associations between sampling year and levels of 3-OHFLUO and 9-OHFLUO suggest potential regulatory impacts. Additionally, higher educational levels were inversely associated with 3-OHFLUO exposure, indicating reduced exposure among individuals with greater education. For clarity and illustrative purposes, the sample matrix has been omitted from this figure. However, the complete details of this model are provided in Table S20 within the supplementary material for reference.

Fig. 12. Phenanthrene metabolites. Determinants of exposure to phenanthrene metabolites, including the statistically significant contribution of tobacco products (smoking and passive smoking). The type of sample (e.g., urine-spot, urine-24 h, or morning urine) significantly influenced exposure levels for nearly all metabolites except 2-OHPHEN, but for illustration purposes it is not included in this figure. Sampling year was a significant factor for all metabolites except 1-OHPHEN and 4-OHPHEN, with both positive and negative associations to be observed. Gender differences influenced exposure levels for most metabolites (excluding 2-OHPHEN and 3-OHPHEN), with higher exposure levels observed among females. Additionally, urbanization was inversely associated only with exposure to 3-OHPHEN, highlighting the complex interplay of lifestyle and environmental factors. For clarity and illustrative purposes, the sample matrix has been omitted from this figure. However, the complete details of this model are provided in Table S21 within the supplementary material for reference.

comparing individual or subgroup concentrations across major demographic dimensions. Our findings highlight significant PAH exposure across Europe, with particularly notable levels of the naphthalene metabolites 2-OHNAP and 1-OHNAP, indicating widespread exposure to substances classified as potentially carcinogenic (Group 2B by IARC). However, a more comprehensive evaluation, such as e.g., exposure reconstruction, is necessary to accurately assess the associated risks and cancer potential linked to naphthalene exposure. Furthermore, it is important to address the existing gap in Human Biomonitoring Guidance Values (HBMGVs), which are currently absent, in order to enable robust risk assessments for the PAHs in the future.

Country-specific stratification reveals heterogeneity in creatinine-adjusted metabolite levels illustrating the varied exposure landscape across Europe. Geographical analysis indicates regional disparities in exposure, especially higher metabolite levels in northern regions, hinting at specific regional PAH sources. Stratification by sex did not reveal

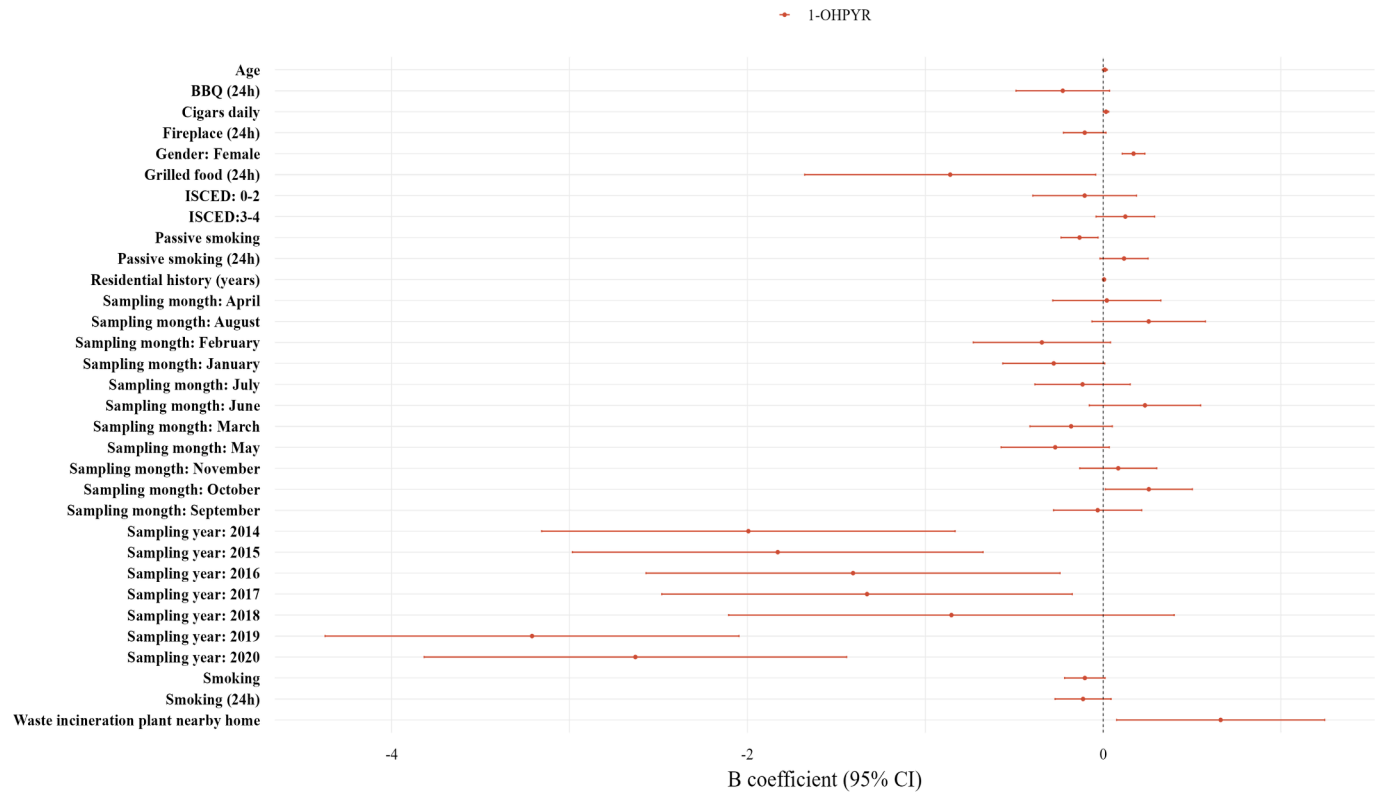

Fig. 13. Pyrene metabolites. Determinants of exposure to pyrene, highlighting the significant contributions of gender and smoking in any form. Females were observed to have higher exposure levels. Smoking habits significantly influenced exposure levels, along with the year of sample collection, with more recent samples showing lower levels of 1-OHPYR. Dietary habits, particularly the consumption of grilled food, and exposure to open fires (e.g., fireplaces or barbecues) were also significant contributors to pyrene exposure patterns.

significant differences in exposure; however, gender, more specifically females, was identified as a determinant of exposure for nearly all PAH metabolites in the multivariate linear regression modeling. In contrast, variations in educational level and urbanization suggest that lower education and higher levels of urbanization are associated with increased PAH exposure. Some of the models confirmed this indication but more research needs to be performed in this direction. Notably, smokers show significantly higher PAH levels than non-smokers, underlining the influence of smoking habits on exposure. Multivariate analysis shows that any kind of smoking exposure is a significant contributor to PAH exposure. Additionally, smoked food, meat and exposure to places with smoke also contribute significantly to the exposure levels. These insights not only show the necessity to develop Human Biomonitoring Guidance Values (HBM-GVs) for selected PAHs and support regulatory actions to further reduce the exposure to this group of substances but also pinpoint areas necessitating further investigation, including the effects of PAHs in human health.

HBM is one of the cornerstones in the chemical strategy for sustainability because it may provide direct measurable insights into the exposure of humans to environmental chemicals and potential health effects. It bridges the gaps in environmental contamination and human health through the assessment of the presence of chemical substances, and their metabolites, in biological matrices (e.g., urine). This approach not only provides identification of emerging risks but also underpins regulatory frameworks by providing real data that inform exposure limits and safety standards. The HBM even allows for effectiveness assessment of policy measures taken for reducing harmful exposures, such as hazardous substance restrictions. Through an environmental policy perspective concerning sustainable development, HBM allows evidence-based decisions on the proper design of benign chemicals to attain aims regarding the protection of public health while minimizing damage to the environment.

Informed consent statement

All participants in the study granted their informed consent Gilles et al. (2022) furnish comprehensive details regarding the ethics committees involved.

CRediT authorship contribution statement

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109383.

Data availability

Data will be made available on request.

References

Abdel-Shafy, H.I., Mansour, M.S., 2016. A review on polycyclic aromatic hydrocarbons: source, environmental impact, effect on human health and remediation. Egypt. J. Pet. 25, 107–123. https://doi.org/10.1016/j.ejpe.2015.03.011.

Akpambang, V., Purcaro, G., Lajide, L., Amoo, I., Conte, L., Moret, S., 2009. Determination of polycyclic aromatic hydrocarbons (PAHs) in commonly consumed Nigerian smoked/grilled fish and meat. Food Addit. Contam. 26, 1096–1103. https://doi.org/10.1080/02652030902855406.

Alkerwi, A.A., Pastore, J., Sauvageot, N., Coroller, G.L., Bocquet, V., D'Incau, M., Aguayo, G., Appenzeller, B., Bejko, D., Bohn, T., 2019. Challenges and benefits of integrating diverse sampling strategies in the observation of cardiovascular risk factors (ORISCAV-LUX 2) study. BMC Med. Res. Method. 19, 1–10. https://doi.org/10.1186/s12874-019-0669-0.

Amarillo, A.C., Carreras, H., 2016. Quantifying the influence of meteorological variables on particle-bound PAHs in urban environments. Atmos. Pollut. Res. 7, 597–602. https://doi.org/10.1016/j.apr.2016.02.006.

Andersen, M.H.G., Saber, A.T., Pedersen, J.E., Pedersen, P.B., Clausen, P.A., Løhr, M., Kermanizadeh, A., Loft, S., Ebbehøj, N.E., Hansen, Å.M., 2018. Assessment of polycyclic aromatic hydrocarbon exposure, lung function, systemic inflammation, and genotoxicity in peripheral blood mononuclear cells from firefighters before and after a work shift. Environ. Mol. Mutagen. 59, 539–548. https://doi.org/10.1002/em.22193.

Arey, J., Atkinson, R., 2003. Photochemical reactions of PAHs in the atmosphere. In: PAHs: An ecotoxicological perspective, 47–63. https://onlinelibrary.wiley.com/doi/pdf/10.1002/0470867132#page=54.

Aydin, Y.M., Kara, M., Dumanoglu, Y., Odabasi, M., Elbir, T., 2014. Source apportionment of polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) in ambient air of an industrial region in Turkey. Atmos. Environ. 97, 271–285. https://doi.org/10.1016/j.atmosenv.2014.08.032.

Badlam, J.B., Badesch, D., Brittain, E., Cordell, S., Ding, T., Fox, K., Hemnes, A., Loyd, J., Pugh, M., Robbins, I., Yu, C., Austin, E.D., 2020. Sex hormone exposure and reproductive factors in pulmonary arterial hypertension: a case-control study. Pulm Circ 10. https://doi.org/10.1177/2045894020908786.

Barbeau, D., Lutier, S., Bonneterre, V., Persoons, R., Marques, M., Herve, C., Maitre, A., 2015. Occupational exposure to polycyclic aromatic hydrocarbons: relations between atmospheric mixtures, urinary metabolites and sampling times. Int. Arch. Occup. Environ. Health 88, 1119–1129. https://doi.org/10.1007/s00420-015-1042-1.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the US population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200. https://doi.org/10.1289/ehp.7337.

Burkhardt, T., Scherer, M., Scherer, G., Pluym, N., Weber, T., Kolossa-Gehring, M., 2023. Time trend of exposure to secondhand tobacco smoke and polycyclic aromatic hydrocarbons between 1995 and 2019 in Germany-Showcases for successful European legislation. Environ. Res. 216, 114638. https://doi.org/10.1016/j.envres.2022.114638.

Busch, A.S., Ljubicic, M.L., Upners, E.N., Fischer, M.B., Kolby, N., Eckert-Lind, C., Jespersen, K., Andersson, A.M., Frederiksen, H., Johannsen, T.H., 2021. Cohort profile: the COPENHAGEN minipuberty study—a longitudinal prospective cohort of healthy full-term infants and their parents. Paediatr. Perinat. Epidemiol. 35, 601–611. https://doi.org/10.1111/ppe.12777.

Campo, L., Polledri, E., Bechtold, P., Gatti, G., Quattrini, G., Olgiati, L., Romolo, M., Ranzi, A., Lauriola, P., Carrozzi, G., 2018. ETS exposure and PAH body burden in nonsmoking Italian adults. Int. J. Environ. Res. Public Health 15, 1156. https://doi.org/10.3390/ijerph15061156.

Cao, Z., Wang, M., Chen, Q., Zhu, C., Jie, J., Li, X., Dong, X., Miao, Z., Shen, M., Bu, Q., 2019. Spatial, seasonal and particle size dependent variations of PAH contamination in indoor dust and the corresponding human health risk. Sci. Total Environ. 653, 423–430. https://doi.org/10.1016/j.scitotenv.2018.10.413.

Chen, H., Ma, S., Yu, Y., Liu, R., Li, G., Huang, H., An, T., 2019. Seasonal profiles of atmospheric PAHs in an e-waste dismantling area and their associated health risk considering bioaccessible PAHs in the human lung. Sci. Total Environ. 683, 371–379. https://doi.org/10.1016/j.scitotenv.2019.04.385.

Cong, L., Fang, Y., He, M., Wang, X., Kannan, N., Li, D., 2010. Ice phase as an important factor on the seasonal variation of polycyclic aromatic hydrocarbons in the Tumen River, Northeastern of China. Environ. Sci. Pollut. Res. 17, 1379–1387. https://doi.org/10.1007/s11356-010-0324-0.

Dat, N.-D., Chang, M.B., 2017. Review on characteristics of PAHs in atmosphere, anthropogenic sources and control technologies. Sci. Total Environ. 609, 682–693. https://doi.org/10.1016/j.scitotenv.2017.07.204.

Dat, N.-D., Lyu, J.-M., Chang, M.-B., 2018. Variation of atmospheric PAHs in northern Taiwan during winter and summer seasons. Aerosol Air Qual. Res. 18, 1019–1031. https://doi.org/10.4209/aaqr.2018.01.0038.

Delgado-Saborit, J.M., Aquilina, N., Baker, S., Harrad, S., Meddings, C., Harrison, R.M., 2010. Determination of atmospheric particulate-phase polycyclic aromatic hydrocarbons from low volume air samples. Anal. Methods 2, 231–242. https://doi.org/10.1039/B9AY00157C.

Dobraca, D., Laurent, C.A., Greenspan, L.C., Hiatt, R.A., Sjödin, A., Kushi, L.H., Windham, G.C., 2020. Urinary polycyclic aromatic hydrocarbons in relation to anthropometric measures and pubertal development in a cohort of Northern California girls. Environ. Epidemiol. 4. https://doi.org/10.1097/EE9.0000000000000102.

Du, T., Shen, X., Zhan, R., 2024. Association of mixed polycyclic aromatic hydrocarbons exposure with cardiovascular disease and the mediating role of inflammatory indices in US adults. Environ. Health Prev. Med. 29, 70. https://doi.org/10.1265/ehpm.24-00091.

ECHA, 2016. Support document for identification of benzo[def]chrysene (benzo[a]pyrene) as a substance of very high concern because of its carcinogenic (article 57 a), mutagenic (article 57 b), toxic for reproduction (article 57 c), persistent, bioaccumulative, and toxic (pbt) (article 57 d) and very persistent and very bioaccumulative (article 57 e) properties. In: SVHC support document –benzo[def]chrysene (benzo[a]pyrene). https://echa.europa.eu/documents/10162/985e117f-38e2-4d45-9d0c-94413dd0462e.

Efsa, 2008. Polycyclic aromatic hydrocarbons in food-scientific opinion of the panel on contaminants in the food chain. EFSA J. 6, 724. https://doi.org/10.2903/j.efsa.2008.724.

Efsa, 2010. Management of left-censored data in dietary exposure assessment of chemical substances. EFSA J. 8, 1557. https://doi.org/10.2903/j.efsa.2010.1557.

Eiguren-Fernandez, A., Avol, E.L., Thurairatnam, S., Hakami, M., Froines, J.R., Miguel, A.H., 2007. Seasonal influence on vapor-and particle-phase polycyclic aromatic hydrocarbon concentrations in school communities located in Southern California. Aerosol Sci. Tech. 41, 438–446. https://doi.org/10.1080/02786820701213511.

Esteban López, M., Göen, T., Mol, H., Nübler, S., Haji-Abbas-Zarrabi, K., Koch, H.M., Kasper-Sonnenberg, M., Dvorakova, D., Hajslova, J., Antignac, J.-P., Vaccher, V.,

Elbers, I., Thomsen, C., Vorkamp, K., Pedraza-Díaz, S., Kolossa-Gehring, M., Castaño, A., 2021. The European human biomonitoring platform - design and implementation of a laboratory quality assurance/quality control (QA/QC) programme for selected priority chemicals. Int. J. Hyg. Environ. Health 234, 113740. https://doi.org/10.1016/j.ijheh.2021.113740.

European Commission, 2014. A harmonised definition of cities and rural areas: the new degree of urbanisation. https://ec.europa.eu/regional_policy/sources/work/2014_01_new_urban.pdf.

Falcon-Rodriguez, C.I., De Vizcaya-Ruiz, A., Rosas-Pérez, I.A., Osornio-Vargas, Á.R., Segura-Medina, P., 2017. Inhalation of concentrated PM2. 5 from Mexico City acts as an adjuvant in a guinea pig model of allergic asthma. Environ. Pollut. 228, 474–483. https://doi.org/10.1016/j.envpol.2017.05.050.

Fernández, S.F., Pardo, O., Hernández, C.S., Garlito, B., Yusà, V., 2021a. Children's exposure to polycyclic aromatic hydrocarbons in the Valencian Region (Spain): urinary levels, predictors of exposure and risk assessment. Environ. Int. 153, 106535. https://doi.org/10.1016/j.envint.2021.106535.

Fernández, S.F., Pardo, O., Pastor, A., Yusà, V., Vento, M., Cernada, M., Gormaz, M., Kuligowski, J., Sánchez, A., Torres, E., 2021b. Biomonitoring of polycyclic aromatic hydrocarbons in the urine of lactating mothers: Urinary levels, association with lifestyle factors, and risk assessment. Environ. Pollut. 268, 115646. https://doi.org/10.1016/j.envpol.2020.115646.

Freire, C., Abril, A., Fernández, M., Ramos, R., Estarlich, M., Manrique, A., Aguirre, A., Ibarluzea, J., Olea, N., 2009. Urinary 1-hydroxypyrene and PAH exposure in 4-year-old Spanish children. Sci. Total Environ. 407, 1562–1569. https://doi.org/10.1016/j.scitotenv.2008.10.068.

Ganzleben, C., Antignac, J.-P., Barouki, R., Castaño, A., Fiddicke, U., Klánová, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int. J. Hyg. Environ. Health 220, 94–97. https://doi.org/10.1016/j.ijheh.2017.01.007.

Georgopoulos, P.G., Sasso, A.F., Isukapalli, S.S., Lioy, P.J., Vallero, D.A., Okino, M., Reiter, L., 2009. Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. J. Eposure Sci. Environ. Epidemiol. 19, 149–171. https://doi.org/10.1038/jes.2008.9.

Gilles, L., Govarts, E., Rambaud, L., Vogel, N., Castaño Esteban, A., López, M., Rodriguez Martin, L., Koppen, G., Remy, S., Vrijheid, M., Montazeri, P., Birks, L., Sepai, O., Stewart, I., Fiddicke, U., Loots, I., Knudsen, L.E., Kolossa-Gehring, M., Schoeters, G., 2021. HBM4EU combines and harmonises human biomonitoring data across the EU, building on existing capacity – the HBM4EU survey. Int. J. Hyg. Environ. Health 237, 113809. https://doi.org/10.1016/j.ijheh.2021.113809.

Gilles, L., Govarts, E., Rodriguez Martin, L., Andersson, A.-M., Appenzeller, B.M.R., Barbone, F., Castaño, A., Coertjens, D., Den Hond, E., Dzhedzheia, V., Eržen, I., López, M.E., Fábelová, L., Fillol, C., Franken, C., Frederiksen, H., Gabriel, C., Haug, L.S., Horvat, M., Halldórsson, T.I., Janasik, B., Holcer, N.J., Kakucs, R., Karakitsios, S., Katsonouri, A., Klánová, J., Kold-Jensen, T., Kolossa-Gehring, M., Konstantinou, C., Koponen, J., Lignell, S., Lindroos, A.K., Makris, K.C., Mazej, D., Morrens, B., Murínová, Ľ.P., Namorado, S., Pedraza-Diaz, S., Peisker, J., Probst-Hensch, N., Rambaud, L., Rosolen, V., Rucic, E., Rüther, M., Sarigiannis, D., Tratnik, J.S., Standaert, A., Stewart, L., Szigeti, T., Thomsen, C., Tolonen, H., Eiríksdóttir, Á., Van Nieuwenhuyse, A., Verheyen, V.J., Vlaanderen, J., Vogel, N., Wasowicz, W., Weber, T., Zock, J.-P., Sepai, O., Schoeters, G., 2022. Harmonization of human biomonitoring studies in europe: characteristics of the HBM4EU-aligned studies participants. J. Environ. Res. Public Health 19, 6787. https://doi.org/10.3390/ijerph19116787.

Govarts, E., Gilles, L., Rodriguez Martin, L., Santonen, T., Apel, P., Alvito, P., Anastasi, E., Andersen, H.R., Andersson, A.-M., Andryskova, L., Antignac, J.-P., Appenzeller, B., Barbone, F., Barnett-Itzhaki, Z., Barouki, R., Berman, T., Bil, W., Borges, T., Buekers, J., Cañas-Portilla, A., Covaci, A., Csako, Z., Den Hond, E., Dvorakova, D., Fabelova, L., Fletcher, T., Frederiksen, H., Gabriel, C., Ganzleben, C., Göen, T., Halldorsson, T.I., Haug, L.S., Horvat, M., Huuskonen, P., Imboden, M., Jagodic Hudobivnik, M., Janasik, B., Janev Holcer, N., Karakitsios, S., Katsonouri, A., Klanova, J., Kokaraki, V., Kold Jensen, T., Koponen, J., Laeremans, M., Laguzzi, F., Lange, R., Lemke, N., Lignell, S., Lindroos, A.K., Lobo Vicente, J., Luijten, M., Makris, K.C., Mazej, D., Melymuk, L., Meslin, M., Mol, H., Montazeri, P., Murawski, A., Namorado, S., Niemann, L., Nübler, S., Nunes, B., Olafsdottir, K., Palkovicova Murinova, L., Papaioannou, N., Pedraza-Diaz, S., Piler, P., Plichta, V., Poteser, M., Probst-Hensch, N., Rambaud, L., Rauscher-Gabernig, E., Rausova, K., Remy, S., Riou, M., Rosolen, V., Rousselle, C., Rüther, M., Sarigiannis, D., Silva, M.J., Šlejkovec, Z., Snoj Tratnik, J., Stajnko, A., Szigeti, T., Tarazona, J.V., Thomsen, C., Tkalec, Ž., Tolonen, H., Trnovec, T., Uhl, M., Van Nieuwenhuyse, A., Vasco, E., Verheyen, V.J., Viegas, S., Vinggaard, A.M., Vogel, N., Vorkamp, K., Wasowicz, W., Weber, T., et al., 2023. Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021). Int. J. Hyg. Environ. Health 249, 114119. https://doi.org/10.1016/j.ijheh.2023.114119.

Guo, H., Huang, K., Zhang, X., Zhang, W., Guan, L., Kuang, D., Deng, Q., Deng, H., Zhang, X., He, M., 2014. Women are more susceptible than men to oxidative stress and chromosome damage caused by polycyclic aromatic hydrocarbons exposure. Environ. Mol. Mutagen. 55, 472–481. https://doi.org/10.1002/em.21866.

Hartwig, A., 2013. Polycyclic Aromatic Hydrocarbons (PAH), MAK Value Documentation 2012. Wiley-VCH, Weinheim.

Hecht, S.S., Carmella, S.G., Yoder, A., Chen, M., Li, Z.-Z., Le, C., Dayton, R., Jensen, J., Hatsukami, D.K., 2006. Comparison of polymorphisms in genes involved in polycyclic aromatic hydrocarbon metabolism with urinary phenanthrene metabolite ratios in smokers. Cancer Epidemiol. Biomark. Prev. 15, 1805–1811. https://doi.org/10.1158/1055-9965.EPI-06-0173.

Hou, X., Li, R., Wang, J., Wei, D., Yang, X., Liao, W., Yuchi, Y., Liu, X., Huo, W., Mao, Z., 2023. Gender-specific associations between mixture of polycyclic aromatic hydrocarbons and telomere length. Environ. Geochem. Health 45, 9583–9598. https://doi.org/10.1007/s10653-023-01752-z.

Huang, S., Li, Q., Liu, H., Ma, S., Long, C., Li, G., Yu, Y., 2022. Urinary monohydroxylated polycyclic aromatic hydrocarbons in the general population from 26 provincial capital cities in China: levels, influencing factors, and health risks. Environ. Int. 160, 107074. https://doi.org/10.1016/j.envint.2021.107074.

Jacob, J., Grimmer, G., Dettbarn, G., 1999. Profile of urinary phenanthrene metabolites in smokers and non-smokers. Biomarkers 4, 319–327. https://doi.org/10.1080/135475099230705.

Jesus, F., Pereira, J.L., Campos, I., Santos, M., Ré, A., Keizer, J., Nogueira, A., Gonçalves, F.J., Abrantes, N., Serpa, D., 2022. A review on polycyclic aromatic hydrocarbons distribution in freshwater ecosystems and their toxicity to benthic fauna. Sci. Total Environ. 153282. https://doi.org/10.1016/j.scitotenv.2022.153282.

Joksić, A.Š., Tratnik, J.S., Mazej, D., Kocman, D., Stajnko, A., Eržen, I., Horvat, M., 2022. Polycyclic aromatic hydrocarbons (PAHs) in men and lactating women in Slovenia: results of the first national human biomonitoring. Int. J. Hyg. Environ. Health 241, 113943. https://doi.org/10.1016/j.ijheh.2022.113943.

Jongeneelen, F.J., 2014. A guidance value of 1-hydroxypyrene in urine in view of acceptable occupational exposure to polycyclic aromatic hydrocarbons. Toxicol. Lett. 231, 239–248. https://doi.org/10.1016/j.toxlet.2014.05.001.

Kakavandi, B., Rafiemanesh, H., Giannakis, S., Beheshtaeen, F., Samoili, S., Hashemi, M., Abdi, F., 2023. Establishing the relationship between Polycyclic Aromatic Hydrocarbons (PAHs) exposure and male infertility: a systematic review. Ecotoxicol. Environ. Saf. 250, 114485. https://doi.org/10.1016/j.ecoenv.2022.114485.

Kameda, T., 2011. Atmospheric chemistry of polycyclic aromatic hydrocarbons and related compounds. J. Health Sci. 57, 504–511. https://doi.org/10.1248/jhs.57.504.

Kameda, Y., Shirai, J., Komai, T., Nakanishi, J., Masunaga, S., 2005. Atmospheric polycyclic aromatic hydrocarbons: size distribution, estimation of their risk and their depositions to the human respiratory tract. Sci. Total Environ. 340, 71–80. https://doi.org/10.1016/j.scitotenv.2004.08.009.

Karakoltzidis, A., Battistelli, C., Bossa, C., Bouman, E.A., Garmendia Aguirre, I., Iavicoli, I., Zare Jeddi, M., Karakitsios, S., Leso, V., Løfstedt, M., Magagna, B., Sarigiannis, D., Schultes, E., Soeteman-Hernandez, L.G., Subramanian, V., Nymark, P., 2024. The FAIR principles as a key enabler to operationalize safe and sustainable by design approaches. RSC Sustain. https://doi.org/10.1039/D4SU00171K.

Karakoltzidis, A., Agalliadou, A., Kermenidou, M., Nikiforou, F., Chatzimpaloglou, A., Feleki, E., Karakitsios, S., Gotti, A., Sarigiannis, D., 2025a. Agent-based modelling: a stochastic approach to assessing personal exposure to environmental pollutants – insights from the URBANOME project. Sci. Total Environ. 967. https://doi.org/10.1016/j.scitotenv.2025.178804.

Karakoltzidis, A., Karakitsios, S.P., Sarigiannis, D.A., 2025b. AI-driven parametrization of michaelis-menten maximal velocity: advancing in silico new approach methodologies (NAMs). NAM J. 100012. https://doi.org/10.1016/j.namjnl.2025.100012.

Kim, K.-H., Jahan, S.A., Kabir, E., Brown, R.J., 2013. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ. Int. 60, 71–80. https://doi.org/10.1016/j.envint.2013.07.019.

Kim, U.J., Karthikraj, R., 2021. Solid-phase microextraction for the human biomonitoring of environmental chemicals: current applications and future perspectives. J. Sep. Sci. 44, 247–273. https://doi.org/10.1002/jssc.202000830.

Klotz, K., Schindler, B.K., Angerer, J., 2011. 1, 2-Dihydroxynaphthalene as biomarker for a naphthalene exposure in humans. Int. J. Hyg. Environ. Health 214, 110–114. https://doi.org/10.1016/j.ijheh.2010.11.003.

Kolossa-Gehring, M., Becker, K., Conrad, A., Schröter-Kermani, C., Schulz, C., Seiwert, M., 2012. Environmental surveys, specimen bank and health related environmental monitoring in Germany. Int. J. Hyg. Environ. Health 215, 120–126. https://doi.org/10.1016/j.ijheh.2011.10.013.

Landis, M.S., Studabaker, W.B., Pancras, J.P., Graney, J.R., Puckett, K., White, E.M., Edgerton, E.S., 2019. Source apportionment of an epiphytic lichen biomonitor to elucidate the sources and spatial distribution of polycyclic aromatic hydrocarbons in the Athabasca Oil Sands Region, Alberta, Canada. Sci. Total Environ. 654, 1241–1257. https://doi.org/10.1016/j.scitotenv.2018.11.131.

Lemke, N., Murawski, A., Lange, R., Weber, T., Apel, P., Dębiak, M., Koch, H.M., Kolossa-Gehring, M., 2021. Substitutes mimic the exposure behaviour of REACH regulated phthalates–a review of the German HBM system on the example of plasticizers. Int. J. Hyg. Environ. Health 236, 113780. https://doi.org/10.1016/j.ijheh.2021.113780.

Lermen, D., Schmitt, D., Bartel-Steinbach, M., Schröter-Kermani, C., Kolossa-Gehring, M., Von Briesen, H., Zimmermann, H., 2014. A new approach to standardize multicenter studies: mobile lab technology for the German Environmental Specimen Bank. PLoS One 9, e105401. https://doi.org/10.1371/journal.pone.0105401.

Lermen, D., Bartel-Steinbach, M., Gwinner, F., Conrad, A., Weber, T., Von Briesen, H., Kolossa-Gehring, M., 2019. Trends in characteristics of 24-h urine samples and their relevance for human biomonitoring studies–20 years of experience in the German Environmental Specimen Bank. Int. J. Hyg. Environ. Health 222, 831–839. https://doi.org/10.1016/j.ijheh.2019.04.009.

Leso, V., Rydberg, T., Halling, M., Karakitsios, S., Nikiforou, F., Karakoltzidis, A., Sarigiannis, D.A., Iavicoli, I., 2024. Safety and sustainability by design: an explorative survey on concepts' knowledge and application. Environ Sci Policy 162, 103909. https://doi.org/10.1016/j.envsci.2024.103909.

Li, X., Li, P., Yan, L., Chen, J., Cheng, T., Xu, S., 2011. Characterization of polycyclic aromatic hydrocarbons in fog–rain events. J. Environ. Monit. 13, 2988–2993. https://doi.org/10.1039/C1EM10543D.

Li, W., Park, R., Alexandrou, N., Dryfhout-Clark, H., Brice, K., Hung, H., 2021. Multi-year analyses reveal different trends, sources, and implications for source-related human health risks of atmospheric polycyclic aromatic hydrocarbons in the Canadian Great Lakes Basin. Environ. Sci. Tech. 55, 2254–2264. https://doi.org/10.1021/acs.est.0c07079.

Li, Z., Sandau, C.D., Romanoff, L.C., Caudill, S.P., Sjodin, A., Needham, L.L., Patterson Jr, D.G., 2008. Concentration and profile of 22 urinary polycyclic aromatic hydrocarbon metabolites in the US population. Environ. Res. 107, 320–331. https://doi.org/10.1016/j.envres.2008.01.013.

Lin, Y., Qiu, X., Yu, N., Yang, Q., Araujo, J.A., Zhu, Y., 2016. Urinary metabolites of polycyclic aromatic hydrocarbons and the association with lipid peroxidation: a biomarker-based study between Los Angeles and Beijing. Environ. Sci. Tech. 50, 3738–3745. https://doi.org/10.1021/acs.est.5b04629.

Liu, C., Wu, M., Fu, M., Wang, H., Nie, J., 2021. Dose–response relationships between polycyclic aromatic hydrocarbon exposure and blood cell counts among coke oven workers: a sex-stratified analysis. BMJ Open 11, e046843. https://doi.org/10.1136/bmjopen-2020-046843.

Liu, C., Liu, Q., Song, S., Li, W., Feng, Y., Cong, X., Ji, Y., Li, P., 2023. The Association between internal polycyclic aromatic hydrocarbons exposure and risk of Obesity—a systematic review with meta-analysis. Chemosphere 138669. https://doi.org/10.1016/j.chemosphere.2023.138669.

Louro, H., Gomes, B.C., Saber, A.T., Iamiceli, A.L., Göen, T., Jones, K., Katsonouri, A., Neophytou, C.M., Vogel, U., Ventura, C., 2022. The use of human biomonitoring to assess occupational exposure to PAHs in Europe: a comprehensive review. Toxics 10, 480. https://doi.org/10.3390/toxics10080480.

Luo, K., Luo, X., Cao, W., Hochalter, J.B., Paiano, V., Sipe, C.J., Carmella, S.G., Murphy, S.E., Jensen, J., Lam, S., 2021. Cigarette smoking enhances the metabolic activation of the polycyclic aromatic hydrocarbon phenanthrene in humans. Carcinogenesis 42, 570–577. https://doi.org/10.1093/carcin/bgaa137.

Ma, Y., Harrad, S., 2015. Spatiotemporal analysis and human exposure assessment on polycyclic aromatic hydrocarbons in indoor air, settled house dust, and diet: a review. Environ. Int. 84, 7–16. https://doi.org/10.1016/j.envint.2015.07.006.

Mallah, M.A., Changxing, L., Mallah, M.A., Noreen, S., Liu, Y., Saeed, M., Xi, H., Ahmed, B., Feng, F., Mirjat, A.A., 2022. Polycyclic aromatic hydrocarbon and its effects on human health: an updated review. Chemosphere 133948. https://doi.org/10.1016/j.chemosphere.2022.133948.

Mannino, M.R., Orecchio, S., 2008. Polycyclic aromatic hydrocarbons (PAHs) in indoor dust matter of Palermo (Italy) area: extraction, GC–MS analysis, distribution and sources. Atmos. Environ. 42, 1801–1817. https://doi.org/10.1016/j.atmosenv.2007.11.031.

Motorykin, O., Schrlau, J., Jia, Y., Harper, B., Harris, S., Harding, A., Stone, D., Kile, M., Sudakin, D., Simonich, S.L.M., 2015. Determination of parent and hydroxy PAHs in personal PM2. 5 and urine samples collected during Native American fish smoking activities. Sci. Total Environ. 505, 694–703. https://doi.org/10.1016/j.scitotenv.2014.10.051.

Murawski, A., Roth, A., Schwedler, G., Schmied-Tobies, M.I., Rucic, E., Pluym, N., Scherer, M., Scherer, G., Conrad, A., Kolossa-Gehring, M., 2020. Polycyclic aromatic hydrocarbons (PAH) in urine of children and adolescents in Germany–human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V). Int. J. Hyg. Environ. Health 226, 113491. https://doi.org/10.1016/j.ijheh.2020.113491.

Nguyen, T.N.T., Jung, K.-S., Son, J.M., Kwon, H.-O., Choi, S.-D., 2018. Seasonal variation, phase distribution, and source identification of atmospheric polycyclic aromatic hydrocarbons at a semi-rural site in Ulsan, South Korea. Environ. Pollut. 236, 529–539. https://doi.org/10.1016/j.envpol.2018.01.080.

Nübler, S., López, M.E., Castaño, A., Mol, H.G., Müller, J., Schäfer, M., Haji-Abbas-Zarrabi, K., Hajslova, J., Pulkrabova, J., Dvorakova, D., 2023. External Quality Assurance Schemes (EQUASs) and Inter-laboratory Comparison Investigations (ICIs) for human biomonitoring of polycyclic aromatic hydrocarbon (PAH) biomarkers in urine as part of the quality assurance programme under HBM4EU. Int. J. Hyg. Environ. Health 250, 114169. https://doi.org/10.1016/j.ijheh.2023.114169.

Nyström, J., 2018. The OSPAR list of chemicals for priority action: Suggestions for future actions. https://www.diva-portal.org/smash/record.jsf?pid=diva2%3A1274202&dswid=-9962.

O'Brien, K.M., Upson, K., Cook, N.R., Weinberg, C.R., 2016. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. Environ. Health Perspect. 124, 220–227. https://doi.org/10.1289/ehp.1509693.

O'Brien, K.M., Upson, K., Buckley, J.P., 2017. Lipid and creatinine adjustment to evaluate health effects of environmental exposures. Curr. Environ. Health Rep. 4, 44–50. https://doi.org/10.1007/s40572-017-0122-7.

Onyemauwa, F., Rappaport, S.M., Sobus, J.R., Gajdošová, D., Wu, R.A., Waidyanatha, S., 2009. Using liquid chromatography–tandem mass spectrometry to quantify monohydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. J. Chromatogr. B 877, 1117–1125. https://doi.org/10.1016/j.jchromb.2009.02.067.

Pack, L.K., Gilles, L., Cops, J., Tolonen, H., van Kamp, I., Esteban-López, M., Pedraza-Díaz, S., Lacasaña, M., Alzaga, B.G., Lermen, D., Bartel-Steinbach, M., Katsonouri, A., Fiddicke, U., Castaño, A., Kolossa-Gehring, M., 2023. A step towards harmonising human biomonitoring study setup on European level: Materials provided and lessons learnt in HBM4EU. Int. J. Hyg. Environ. Health 249, 114118. https://doi.org/10.1016/j.ijheh.2023.114118.

Palazzi, P., Hardy, E.M., Appenzeller, B.M., 2019. Biomonitoring of children exposure to urban pollution and environmental tobacco smoke with hair analysis–a pilot study on children living in Paris and Yeu Island, France. Sci. Total Environ. 665, 864–872. https://doi.org/10.1016/j.scitotenv.2019.02.177.

Patel, Y.M., Park, S.L., Carmella, S.G., Paiano, V., Olvera, N., Stram, D.O., Haiman, C.A., Le Marchand, L., Hecht, S.S., 2016. Metabolites of the polycyclic aromatic hydrocarbon phenanthrene in the urine of cigarette smokers from five ethnic groups with differing risks for lung cancer. PLoS One 11, e0156203. https://doi.org/10.1371/journal.pone.0156203.

Piler, P., Kandrnal, V., Kukla, L., Andrýsková, L., Švancara, J., Jarkovský, J., Dušek, L., Pikhart, H., Bobák, M., Klánová, J., 2017. Cohort profile: the european longitudinal study of pregnancy and childhood (ELSPAC) in the Czech Republic. Int. J. Epidemiol. 46, 1379. https://doi.org/10.1093/ije/dyw091.

R Core Team 2009. A language and environment for statistical computing. http://www.R-project.org.

Rafiee, A., Hoseini, M., Akbari, S., Mahabee-Gittens, E.M., 2023. Exposure to Polycyclic Aromatic Hydrocarbons and adverse reproductive outcomes in women: current status and future perspectives. Rev. Environ. Health. https://doi.org/10.1515/reveh-2022-0182.

Ramesh, A., Archibong, A.E., 2011. Reproductive toxicity of polycyclic aromatic hydrocarbons: occupational relevance. In: Reproductive and Developmental Toxicology. Elsevier.

Ramsauer, B., Sterz, K., Hagedorn, H.-W., Engl, J., Scherer, G., Mcewan, M., Errington, G., Shepperd, J., Cheung, F., 2011. A liquid chromatography/tandem mass spectrometry (LC-MS/MS) method for the determination of phenolic polycyclic aromatic hydrocarbons (OH-PAH) in urine of non-smokers and smokers. Anal. Bioanal. Chem. 399, 877–889. https://doi.org/10.1007/s00216-010-4355-7.

Raponi, F., Bauleo, L., Ancona, C., Forastiere, F., Paci, E., Pigini, D., Tranfo, G., 2017. Quantification of 1-hydroxypyrene, 1-and 2-hydroxynaphthalene, 3-hydroxybenzo [a] pyrene and 6-hydroxynitropyrene by HPLC-MS/MS in human urine as exposure biomarkers for environmental and occupational surveys. Biomarkers 22, 575–583. https://doi.org/10.1080/1354750X.2016.1252959.

Ratelle, M., Khoury, C., Adlard, B., Laird, B., 2020. Polycyclic aromatic hydrocarbons (PAHs) levels in urine samples collected in a subarctic region of the Northwest Territories, Canada. Environ. Res. 182, 109112. https://doi.org/10.1016/j.envres.2020.109112.

Ravindra, K., Sokhi, R., Van Grieken, R., 2008. Atmospheric polycyclic aromatic hydrocarbons: source attribution, emission factors and regulation. Atmos. Environ. 42, 2895–2921. https://doi.org/10.1016/j.atmosenv.2007.12.010.

Rombolà, A.G., Fabbri, D., Baronti, S., Vaccari, F.P., Genesio, L., Miglietta, F., 2019. Changes in the pattern of polycyclic aromatic hydrocarbons in soil treated with biochar from a multiyear field experiment. Chemosphere 219, 662–670. https://doi.org/10.1016/j.chemosphere.2018.11.178.

Sampaio, G.R., Guizellini, G.M., Da Silva, S.A., De Almeida, A.P., Pinaffi-Langley, A.C.C., Rogero, M.M., De Camargo, A.C., Torres, E.A., 2021. Polycyclic aromatic hydrocarbons in foods: biological effects, legislation, occurrence, analytical methods, and strategies to reduce their formation. Int. J. Mol. Sci. 22, 6010. https://doi.org/10.3390/ijms22116010.

Schneider, S.L., 2013. The international standard classification of education 2011. In: Class and Stratification Analysis. Emerald Group Publishing Limited.

Sochacka-Tatara, E., Majewska, R., Perera, F.P., Camann, D., Spengler, J., Wheelock, K., Sowa, A., Jacek, R., Mróz, E., Pac, A., 2018. Urinary polycyclic aromatic hydrocarbon metabolites among 3-year-old children from Krakow, Poland. Environ. Res. 164, 212–220. https://doi.org/10.1016/j.envres.2018.02.032.

Soleimani, M., Ebrahimi, Z., Mirghaffari, N., Moradi, H., Amini, N., Poulsen, K.G., Christensen, J.H., 2022. Seasonal trend and source identification of polycyclic aromatic hydrocarbons associated with fine particulate matters (PM 2.5) in Isfahan City, Iran, using diagnostic ratio and PMF model. Environ. Sci. Poll. Res. 1–16. https://doi.org/10.1007/s11356-021-17635-8.

St. Helen, G., Goniewicz, M.L., Dempsey, D., Wilson, M., Jacob III, P., Benowitz, N.L., 2012. Exposure and kinetics of polycyclic aromatic hydrocarbons (PAHs) in cigarette smokers. Chem. Res. Toxicol. 25, 952–964. https://doi.org/10.1021/tx300043k.

Stallings-Smith, S., Mease, A., Johnson, T.M., Arikawa, A.Y., 2018. Exploring the association between polycyclic aromatic hydrocarbons and diabetes among adults in the United States. Environ. Res. 166, 588–594. https://doi.org/10.1016/j.envres.2018.06.041.

Styszko, K., Szramowiat, K., Kistler, M., Giebl, A.K., Socha, S., Rosenberg, E.E., Gołaś, J., 2016. Polycyclic aromatic hydrocarbons and their nitrated derivatives associated with PM10 from Kraków city during heating season. E3S Web Conf. 10, 00091. https://doi.org/10.1051/e3sconf/20161000091.

Sun, K., Song, Y., He, F., Jing, M., Tang, J., Liu, R., 2021. A review of human and animals exposure to polycyclic aromatic hydrocarbons: health risk and adverse effects, photo-induced toxicity and regulating effect of microplastics. Sci. Total Environ. 773, 145403. https://doi.org/10.1016/j.scitotenv.2021.145403.

Suwan-Ampai, P., Navas-Acien, A., Strickland, P.T., Agnew, J., 2009. Involuntary tobacco smoke exposure and urinary levels of polycyclic aromatic hydrocarbons in the United States, 1999 to 2002. Cancer Epidemiol. Biomark. Prev. 18, 884–893. https://doi.org/10.1158/1055-9965.EPI-08-0939.

Tabatabaei, Z., Shamsedini, N., Mohammadpour, A., Baghapour, M.A., Hoseini, M., 2022. Exposure assessment of children living in homes with hookah smoking parents to polycyclic aromatic hydrocarbons: urinary level, exposure predictors, and risk assessment. Environ. Sci. Pollut. Res. 29, 68667–68679. https://doi.org/10.1007/s11356-022-20589-0.

Tennekes, M., 2018. tmap: thematic maps in R. J. Stat. Softw. 84, 1–39. https://doi.org/10.18637/jss.v084.i06.

Thai, P.K., Heffernan, A.L., Toms, L.L., Li, Z., Calafat, A.M., Hobson, P., Broomhall, S., Mueller, J.F., 2016. Monitoring exposure to polycyclic aromatic hydrocarbons in an Australian population using pooled urine samples. Environ Int 88, 30–35. https://doi.org/10.1016/j.envint.2015.11.019.

Thai, P.K., Banks, A.P., Toms, L.-M.-L., Choi, P.M., Wang, X., Hobson, P., Mueller, J.F., 2020. Analysis of urinary metabolites of polycyclic aromatic hydrocarbons and cotinine in pooled urine samples to determine the exposure to PAHs in an Australian

population. Environ. Res. 182, 109048. https://doi.org/10.1016/j.envres.2019.109048.
Umweltbundesamtes 2007. Naphthalin/Naphthole und Human-Biomonitoring. 50, 1357–1364. doi:10.1007/s00103-007-0342-3.
Uppstad, H., Osnes, G.H., Cole, K.J., Phillips, D.H., Haugen, A., Mollerup, S., 2011. Sex differences in susceptibility to PAHs is an intrinsic property of human lung adenocarcinoma cells. Lung Cancer 71, 264–270. https://doi.org/10.1016/j.lungcan.2010.09.006.
Urbancova, K., Lankova, D., Rossner, P., Rossnerova, A., Svecova, V., Tomaniova, M., Veleminsky, J.R.M., Sram, R.J., Hajslova, J., Pulkrabova, J., 2017. Evaluation of 11 polycyclic aromatic hydrocarbon metabolites in urine of Czech mothers and newborns. Sci. Total Environ. 577, 212–219. https://doi.org/10.1016/j.scitotenv.2016.10.165.
Urbancova, K., Dvorakova, D., Gramblicka, T., Sram, R.J., Hajslova, J., Pulkrabova, J., 2020. Comparison of polycyclic aromatic hydrocarbon metabolite concentrations in urine of mothers and their newborns. Sci. Total Environ. 723, 138116. https://doi.org/10.1016/j.scitotenv.2020.138116.
Van Buuren, S., Groothuis-Oudshoorn, K., 2011. mice: Multivariate imputation by chained equations in R. J. Stat. Softw. 45, 1–67. https://doi.org/10.18637/jss.v045.i03.
Vicente, J.L., Ganzleben, C., Gasol, R., Marnane, I., Gilles, L., Buekers, J., Bessems, J., Colles, A., Gerofke, A., David, M., 2023. HBM4EU results support the chemicals' strategy for sustainability and the zero-pollution action plan. Int. J. Hyg. Environ. Health 248, 114111. https://doi.org/10.1016/j.ijheh.2023.114111.
Wang, M., Tang, S., Zhang, L., Zhao, Y., Peng, Y., Zheng, S., Liu, Z., 2024. Association between urinary polycyclic aromatic hydrocarbons and risk of metabolic associated fatty liver disease. Int. Arch. Occup. Environ. Health 1–16. https://doi.org/10.1007/s00420-024-02076-w.
Wang, Z., Wang, J., Richter, H., Howard, J.B., Carlson, J., Levendis, Y.A., 2003. Comparative study on polycyclic aromatic hydrocarbons, light hydrocarbons, carbon monoxide, and particulate emissions from the combustion of polyethylene, polystyrene, and poly (vinyl chloride). Energy Fuel 17, 999–1013. https://doi.org/10.1021/ef020269z.
WHO, 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. https://apps.who.int/iris/bitstream/handle/10665/260127/9789289002134-eng.pdf?sequence=1&isAllowed=y.
Wickham, H., 2011. ggplot2. Wiley Interdiscip. Rev. Comput. Stat. 3, 180–185. https://doi.org/10.1002/wics.147.
Xing, W., Gu, W., Liang, M., Wang, Z., Fan, D., Zhang, B., Wang, L., 2023. Sex-specific effect of urinary metabolites of polycyclic aromatic hydrocarbons on thyroid profiles: results from NHANES 2011–2012. Environ. Sci. Pollut. Res. 30, 47168–47181. https://doi.org/10.21203/rs.3.rs-2098253/v1.
Yost, E.E., Galizia, A., Kapraun, D.F., Persad, A.S., Vulimiri, S.V., Angrish, M., Lee, J.S., Druwe, I.L., 2021. Health effects of naphthalene exposure: a systematic evidence map and analysis of potential considerations for dose–response evaluation. Environ. Health Perspect. 129, 076002. https://doi.org/10.1289/EHP7381.
Yuan, J.-M., Gao, Y.-T., Murphy, S.E., Carmella, S.G., Wang, R., Zhong, Y., Moy, K.A., Davis, A.B., Tao, L., Chen, M., 2011. Urinary levels of cigarette smoke constituent metabolites are prospectively associated with lung cancer development in smokers. Cancer Res. 71, 6749–6757. https://doi.org/10.1158/0008-5472.CAN-11-0209.
Zhang, Y., Dong, S., Wang, H., Tao, S., Kiyama, R., 2016. Biological impact of environmental polycyclic aromatic hydrocarbons (ePAHs) as endocrine disruptors. Environ. Pollut. 213, 809–824. https://doi.org/10.1016/j.envpol.2016.03.050.
Zhang, X., Li, Z., 2023. Developing a profile of urinary PAH metabolites among Chinese populations in the 2010s. Sci. Total Environ. 857, 159449. https://doi.org/10.1016/j.scitotenv.2022.159449.
Zhong, Y., Zhu, L., 2013. Distribution, input pathway and soil–air exchange of polycyclic aromatic hydrocarbons in Banshan Industry Park, China. Sci. Total Environ. 444, 177–182. https://doi.org/10.1016/j.scitotenv.2012.11.091.
Zhou, S., Zhu, Q., Liu, H., Jiang, S., Zhang, X., Peng, C., Yang, G., Li, J., Cheng, L., Zhong, R., 2021. Associations of polycyclic aromatic hydrocarbons exposure and its interaction with XRCC1 genetic polymorphism with lung cancer: a case-control study. Environ. Pollut. 290, 118077. https://doi.org/10.1016/j.envpol.2021.118077.
Zhu, L., Lu, H., Chen, S., Amagai, T., 2009. Pollution level, phase distribution and source analysis of polycyclic aromatic hydrocarbons in residential air in Hangzhou, China. J. Hazard. Mater. 162, 1165–1170. https://doi.org/10.1016/j.jhazmat.2008.05.150.
Zhu, X., Meng, Y., Ju, Y., Yang, Y., Zhang, S.E., Miao, L., Liu, Z., 2023. Association of the urinary polycyclic aromatic hydrocarbons with sex hormones stratified by menopausal status older than 20 years: a mixture analysis. Environ. Sci. Pollut. Res. 30, 57717–57727. https://doi.org/10.1007/s11356-023-26099-x.