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Exposure to bisphenol A in European women from 2007 to 2014 using human biomonitoring data – The European Joint Programme HBM4EU

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ABSTRACT

Background: Bisphenol A (BPA; or 4,4′-isopropylidenediphenol) is an endocrine disrupting chemical. It was widely used in a variety of plastic-based manufactured products for several years. The European Food Safety Authority (EFSA) recently reduced the Tolerable Daily Intake (TDI) for BPA by 20,000 times due to concerns about immune-toxicity.

Objective: We used human biomonitoring (HBM) data to investigate the general level of BPA exposure from 2007 to 2014 of European women aged 18–73 years (n = 4,226) and its determinants.

Methods: Fifteen studies from 12 countries (Austria, Belgium, Denmark, France, Germany, Greece, Israel, Luxembourg, Slovenia, Spain, Sweden, and the United Kingdom) were included in the BPA Study protocol developed within the European Joint Programme HBM4EU. Seventy variables related to the BPA exposure were collected through a rigorous post-harmonization process. Linear mixed regression models were used to investigate the determinants of total urine BPA in the combined population.

Results: Total BPA was quantified in 85–100 % of women in 14 out of 15 contributing studies. Only the Austrian PBAT study (Western Europe), which had a limit of quantification 2.5 to 25-fold higher than the other studies (LOQ=2.5 μg/L), found total BPA in less than 5 % of the urine samples analyzed. The geometric mean (GM) of total urine BPA ranged from 0.77 to 2.47 μg/L among the contributing studies. The lowest GM of total BPA was observed in France (Western Europe) from the ELFE subset (GM=0.77 μg/L (0.98 μg/g creatinine), n = 1741), and the highest levels were found in Belgium (Western Europe) and Greece (Southern Europe), from DEMOCOPHES (GM=2.47 μg/L (2.26 μg/g creatinine), n = 129) and HELIX-RHEA (GM=2.47 μg/L (2.44 μg/g creatinine), n = 194) subsets, respectively. One hundred percent of women in 14 out of 15 data collections in this study exceeded the health-based human biomonitoring guidance value for the general population (HBM-GV_{GenPop}) of 0.0115 μg total BPA/L urine derived from the updated EFSA's BPA TDI. Variables related to the measurement of total urine BPA and those related to the main socio-demographic characteristics (age, height, weight, education, smoking status) were collected in almost all studies, while several variables related to BPA exposure factors were not gathered in most of the original studies (consumption of beverages contained in plastic bottles, consumption of canned food or beverages, consumption of food in contact with plastic packaging, use of plastic film or plastic containers for food, having a plastic floor covering in the house, use of thermal paper…). No clear determinants of total urine BPA concentrations among European women were found. A broader range of data planned for collection in the original questionnaires of the contributing studies would have resulted in a more thorough investigation of the determinants of BPA exposure in European women.

Conclusion: This study highlights the urgent need for action to further reduce exposure to BPA to protect the population, as is already the case in the European Union. The study also underscores the importance of pre-harmonizing HBM design and data for producing comparable data and interpretable results at a European-wide level, and to increase HBM uptake by regulatory agencies.

1. Introduction

Bisphenol A (BPA; 80-05-7; or 2,2-Bis(4-hydroxyphenyl)propane or 4,4′-isopropylidenediphenol) was until recent years the most important form of a phenolic organic chemical compound produced and used in Europe. In 2006, the global production of BPA was around 3.8 million tons, of which about 1.15 million tons were consumed in the European Union (European Commission, 2004; 2008). In recent years, BPA has been progressively replaced by substitutes with similar structural properties such as bisphenol S and F (Lehmler et al., 2018; Mustieles et al., 2020). BPA is an endocrine disruptor potentially associated with different adverse effects in humans during the perinatal stage, the childhood stage, and in adults (Rochester, 2013). Epidemiological studies have shown associations between BPA exposure and decreased early language development in toddlers (Vom Saal and Vandenberg, 2021), increased adiposity in young children (Kim et al., 2019), and higher incidence of type 2 diabetes (Hwang et al., 2018; Siddique et al., 2020), cardiovascular or cardio-metabolic diseases (Kang et al., 2023), and reproductive health parameters (Stavridis et al., 2022; Lu et al., 2024) in young adults and adults. Due to its reproductive toxicity and endocrine disrupting properties, BPA was listed as a substance of very high concern (SVHC) under the REACH Candidate List (ECHA, 2018). The Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) is a European Union law to protect human health and the environment from the risks that can be posed by chemicals (https://echa.europa.eu). In 2018, BPA was reclassified as a category 1B reprotoxic substance under the CLP Regulation (a regulation that aligns the European Union's system of Classification, Labeling and Packaging of chemical substances and mixtures with the Globally Harmonized System). Since January 2020, the REACH restriction on the use of BPA in thermal paper has come into effect in all EU countries (ECHA, 2020).

There is unequivocal evidence that virtually the entire population is exposed to BPA, including vulnerable population groups such as pregnant women and children (Casas et al., 2013; Frederiksen et al., 2014; Covaci et al., 2015; Philips et al., 2018; Fillol et al., 2021; Tschersich et al., 2021; Schoeters et al., 2022). BPA has been used for labelling thermal papers and has also been found in personal care products, dental sealants and medical devices (Geens et al., 2011; Geens et al., 2012). Human exposure occurs mainly through dietary intake in the general population, but also via water, air, house dust, and skin contact (Vandenberg et al., 2007; Berman et al., 2014; Lv et al., 2017; Rotimi et al., 2021). BPA has been widely used in the manufacture of food contact materials. It is used in polycarbonate products such as plastic food packaging and plastic bottles, as well as in epoxy resins used for coating and protective films covering food and beverage cans and tins (Munguia-Lopez et al., 2005; Le et al., 2008; Cao et al., 2011). Human exposure to BPA can also occur from clothing textiles, especially those manufactured from polyesters and recycling products (Xue et al., 2017). In addition, adults occupationally exposed to BPA have, most often, higher BPA levels than non-occupationally exposed individuals (He et al., 2009; Ribeiro et al., 2017). Unlike the general population, workers are more likely to be exposed to BPA through direct skin contact or inhalation (Bousoumah et al., 2021).

In 2018, there was no recent Europe-wide survey on BPA exposure since the COPHES/DEMOCOPHES study conducted in 2011–2012 among a population of mother–child pairs across six European countries (Covaci et al., 2015). However, data from numerous existing studies

could be used to evaluate the general level of BPA exposure across several countries through a platform able to implement such an approach. HBM4EU, a European project of human biomonitoring coordination and research that ran from 2017 to 2022 (https://www.hbm4eu.eu/about-hbm4eu/) was such a platform. One of its goals was the development and the implementation of a European Human Biomonitoring Platform to deliver high standard, comparable and robust European data on human internal exposure to chemicals and mixtures of chemicals. In this context, the information platform for chemical monitoring (IPCHEM) (https://ipchem.jrc.ec.europa.eu/) was set up by the European Commission as a single access point to locate and retrieve chemical monitoring data collections (Ganzleben et al., 2017; Comero et al., 2020). Moreover, the European HBM dashboard was elaborated to visualize summary statistics of HBM data collections (https://hbm.vito.be/eu-hbm-dashboard).

HBM4EU is an innovative European HBM project operating at the science-policy interface (Ganzleben et al., 2017; Kolossa-Gehring et al., 2023). Its major goals were to answer open policy relevant questions as defined by the 30 HBM4EU partner countries and EU institutions, to provide policy makers a fast and easy access to data, and to fill knowledge gaps by research. A selection of high-priority substances, taking into account policy needs at national and EU level to better understand chemical exposure and health effects, including bisphenols, was prioritized for action under the HBM4EU Initiative (Ougier et al., 2021a; Vorkamp et al., 2021; Sabbioni et al., 2022). The health-based guidance values for BPA exposure have been under constant review for several years now. Already in 2015, experts at the European Food Safety Authority (EFSA) drastically lowered the Tolerable Daily Intake (TDI) from 50 Âµg per kilogram of body weight per day to a temporary TDI of 4 µg/kg bw/day, a value that also applies to pregnant women and women of childbearing age (EFSA, 2015). Since 2023, based on new scientific evidence assessed (in particular on immune-toxicity concerns, apart from other suspected adverse effects including reprotoxicity, metabolic disruption and neurotoxicity), EFSA's experts established a new TDI of 0.2 ng/kg bw/day, lower by a factor of 20.000 than the previous temporary level (EFSA, 2023).

BPA is excreted in urine in both free (unconjugated) and conjugated forms (Arbuckle et al., 2015). However, in healthy general populations, BPA is excreted mostly in conjugated form (more 90 % within 24 h) (Thayer et al., 2015; Andra et al., 2016). The half-life for terminal elimination of BPA in urine is relatively short in humans, approximately 6 h for total or unconjugated forms (Thayer et al., 2015). Therefore, urinary levels can only reflect recent (<24 h) exposure to BPA. Urine is the most commonly used and preferred matrix for BPA measurement in humans, and the levels in urine are about 10 times higher compared to BPA concentrations measured in serum. Total BPA in urine, meaning the sum of free and conjugated BPA, is a robust marker for the assessment of recent human exposure (Koch et al., 2012). The measurement of both total and unconjugated BPA coupled with conjugated forms can help to understand an external contamination by comparing calculated conjugated BPA with the measured conjugated BPA, which is not related to contamination (Longnecker et al., 2013; Gerona et al., 2016). The measurement of free BPA in urine, where contamination cannot be ruled out, cannot be a reliable indicator for the assessment of human exposure (Koch et al., 2012).

Several studies on BPA exposure have been conducted in European countries in the last decades. These studies included different target populations. As a vulnerable population group, pregnant women in general are by far the most frequently studied population. Most studies have dealt with a single measurement of BPA in blood or in urine (most often in urine). As the majority of available BPA biomonitoring data across European countries concerns urinary BPA concentrations among women, the main objective of this study was to collect these data and to describe and compare the urinary BPA concentrations in women at the European level. The second objective was to explore the determinants of urinary BPA levels in the combined population. The present paper also addresses the main challenges of conducting such a descriptive epidemiological study based on the use of fragmented human biomonitoring (HBM) data of different European studies.

2. Materials and methods

2.1. Study design

This is a descriptive study based on existing HBM data on BPA exposure from studies conducted in Europe between 2007 and 2014 (period covering studies for which BPA data were available in 2018). Individual data from the selected studies were collected through HBM4EU.

A dedicated protocol was developed before starting the study (**Supplementary Material S1**). This protocol presented the general framework of the present BPA Study, the objectives, the method to be implemented, the timeline of the study and the expected collaborations. The study protocol was developed in 2018 and sent to all collaborators (which were mostly the principal investigators) of the eligible studies.

2.2. Inclusion criteria for the present BPA study

Eligible European datasets were collected from all studies focused on the general population, assessed exposure to BPA in urine, included all adult women aged 18 and over, regardless of gestational statuses. The selected studies included prospective and cross-sectional studies, including those that supplied data from different sampling years. Prospective birth cohort studies where maternal levels of urinary BPA were available, and studies targeting pregnant women in general population were also eligible. For studies including both males and females, or mother–child/mother-newborn pairs populations, only data from women sub-samples were utilized. Studies not targeting the general population were not eligible (*e.g.,* clinical population, institutionalized mothers, occupational studies). Eligible studies were only those that focused on urine samples independent of the frequency of sampling (i.e. measurement of BPA in other biological matrices was not eligible). This could be first morning urine sample, 24-hour urine collection, or spot urine sample.

The chemical of interest was the measurement of urinary BPA concentrations (total BPA, free BPA and/or, conjugated BPA). Information was also collected on the analytical methods and materials used for the measurement of BPA in each of the participating studies. The main eligibility criteria were the measurement of BPA concentrations in urine samples from adult women, and the measurement of at least one biological parameter that allows normalizing for urinary dilution (urinary creatinine, specific gravity, or osmolality).

2.3. Inventory of the available studies on BPA exposure in Europe

The eligible HBM studies were identified based on the "HBM4EU metadata overview file for IPCHEM (updated version from June 27, 2018)". This was an extraction of information gathered under the HBM4EU for the IPCHEM Portal. Additional studies were identified based on published manuscripts (see Table 1). The sample collection period was set to run from 2007 to 2018, covering the last 10 years. This was also the time period over which most of the available existing studies on BPA exposure were reported in the "HBM4EU metadata overview file for IPCHEM".

In total, we identified 21 eligible studies from 15 countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Israel, Lithuania, Luxembourg, Norway, Slovenia, Spain, Sweden, and the United Kingdom), and their data owners were all invited to participate in the present BPA Study. Six eligible studies from Austria (IC-HBM study), Finland (RefLim2011 and FINRISK2012 studies), Lithuania (KANC study), Norway (IES study), and Sweden (BAMSE study) were not included for various reasons, *e.g.,* the sharing of individual data was not

Table 1
Overview of the main characteristics of the 15 eligible studies included in the BPA Study (this study).

		Characteristics of the original study[a]									Characteristics of the selected subpopulation sample[b]						
Study collection[c]	Relevant published paper[d]	Country (geographical area)	Data collection period	Study design	Sampling strategy	Coverage area	Type of population	Number of participants	Age of participants	Population representativity (to the coverage area)	Data collection period	Matrix sampling	Sampling tube	Analytical method	Number of BPA samples[e]	Age of participants	Population subsample representativity (to the original sample)
3xG	(Van Den Heuvel et al., 2020)	Belgium (Western Europe)	2010-2015	Longitudinal (birth cohort)	Willing to participate	Local level (3 rural communities in Flanders)	Pregnant women (and their newborns)	301	20-43 years	Yes	2011-2013	First-morning urine	Glass	LC-MS/MS	150	23-40 years	Yes
DEMOCOPHES-Belgium	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Belgium (Western Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	National level (selected areas)	Mother and child pairs	129	27-45 years	No	2011-2012	First-morning urine	Glass	GC-ECNI/MS	129	27-45 years	Yes
DEMOCOPHES-Denmark	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Denmark (Northern Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	National level (selected areas)	Mother and child pairs	145	31-52 years	No	2011-2012	First-morning urine	Polypropylene	Online SPE-LC-MS/MS	145	31-52 years	Yes
DEMOCOPHES-Spain	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Spain (Southern Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	National level (selected areas)	Mother and child pairs	240	26-48 years	No	2011-2012	First-morning urine	Polypropylene	HPLC-MS/MS	115	26-48 years	Yes
DEMOCOPHES-Luxembourg	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Luxembourg (Western Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	National level (selected areas)	Mother and child pairs	60	33-45 years	No	2011-2012	First-morning urine	Polypropylene	LC-MS/MS	60	33-45 years	Yes
DEMOCOPHES-Sweden	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Sweden (Northern Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	National level (selected areas)	Mother and child pairs	200	28-46 years	No	2011-2012	First-morning urine	Polypropylene	LC-MS/MS	98	28-46 years	Yes
DEMOCOPHES-Slovenia	(Becker et al., 2014; Schindler et al., 2014; Covaci et al., 2015; Den Hond et al., 2015)	Slovenia (Southern Europe)	2011-2012	Cross-sectional survey	Stratified clustered sampling	Regional level (selected areas)	Mother and child pairs	156	30-52 years	No	2011-2012	First-morning urine	Polypropylene	GC-MS/MS	107	30-46 years	Yes
ELFE	(Vandentorren et al., 2009; Oleko et al., 2011; Vandentorren et al., 2011; Dereumeaux et al., 2016; Charles et al., 2020)	France (Western Europe)	2011	Longitudinal design	Random selection	National level	Pregnant women	4145	18-44 years	Yes	2011-2011	Urine-spot	Polypropylene	GC-MS/MS	1741	18-44 years	Yes
ESB	(Kolossa-Gehring et al., 2012; Lermen et al., 2014; Lermen et al., 2019)	Germany (Western Europe)	1981-yearly campaings	Other	Convenience /Intentional-Stratified	Local level (Münster, Westf.)	General population	~ 120 per year	20-29 years	No	2008-2009	Urine-24h	Polypropylene	HPLC-MS/MS	60	20-29 years	Yes (all women were selected)
FLEHS 3 Ref Adult	(Schoeters et al., 2017; Van Den Heuvel et al., 2020)	Belgium (Western Europe)	05/2014-12/2014	Cross-sectional survey	Stratified clustered multi-stage design	Regional level (Flanders)	General population	209	50-66 years	Yes	2014-2014	Urine-spot	Glass	GC-MS	101	50-66 years	Yes (all women were selected)
HELIX-BIB	(Wright et al., 2013; Vrijheid et al., 2014; Haug et al., 2018; Maitre et al., 2018; Montazeri et al., 2019)	United Kingdom (Northern Europe)	03/2007-11/2010	Longitudinal (cohort)	Convenience /Intentional	Local level (Bradford)	Pregnant women	13776	16-43 years	Yes	2007-2008	Urine-spot	Polypropylene	e SPE-HPLC-MS/MS	205	18-42 years	Yes (all adults were selected)
HELIX-RHEA	(Vrijheid et al., 2014; Chatzi et al., 2017; Haug et al., 2018; Maitre et al., 2018; Montazeri et al., 2019)	Greece (Southern Europe)	02/2007-02/2008	Longitudinal (cohort)	Convenience /Intentional	Regional level (Heraklion)	Pregnant women	1610	16-43 years	Yes	2007-2008	Urine-spot	Polypropylene	e SPE-HPLC-MS/MS	194	18-42 years	Yes (all adults were selected)
IBS	(Berman et al., 2013; 2014)	Israel (other)	02/2011-06/2011	Cross-sectional survey	Convenience /Intentional	National level	General population	249	20-74 years	No	2011-2011	Urine-spot	Polypropylene	GC-MS/MS	117	24-73 years	Yes (all adult women were selected)
OCC	(Frederiksen et al., 2014; Kyhl et al., 2015; Jensen et al., 2019)	Denmark (Northern Europe)	01/2010-12/2030	Longitudinal design	Random selection-Stratified	Regional level (Odense)	Pregnant women	2500 planned	18-43 years	Yes	2010-2013	First-fasting morning urine	Glass	Online SPE-LC-MS/MS	842	19-43 years	Yes
PBAT	(Hartmann et al., 2015; Hartmann et al., 2016)	Austria (Western Europe)	01/2010-03/2012	Cross-sectional survey	Random selection-Stratified	National level	General population	595	6-81 years	Yes	2010-2011	Urine-spot	Polypropylene and Aluminium	e SPE-HPLC-MS/MS	162	18-64 years	Yes (all adult women were selected)

[a]Based on characteristics from the original primary study.
[b]Sub-samples fulfilling the selection criteria for the present BPA Study.
[c]Meaning of the acronym of the contributing study: 3xG (or 'drie maal G') = Gezonheid Gementen Geboorten (https://studie3xg.be/nl); BIB=Born in Bradford; DEMOCOPHES=Demonstration of a study to coordinate and perform human biomonitoring on a European scale; ELFE = Étude Longitudinale Française depuis l'Enfance (https://www.elfe-france.fr/); ESB=Environmental Specimen Bank; FLEHS=Flemish Environment and Health Study; HELIX=Human Early Life Exposome; IBS=Israeli Biomonitoring Study; OCC=Odense Child Cohort; PBAT=Phthalates and Bisphenol A Exposure in Austria; and RHEA = "The 'RHEA' cohort name is inspired by 'Péα' the mythological wife of Kronos (Cronus)".
[d]Papers related to the overall study collection and/or the original targeted population, and not only the papers focused on BPA data collection.
[e]Single measurement of BPA concentration per participant's urine sample.

possible (non-consent from the original study protocol), a data sharing agreement could not be signed, or sampling was still in progress. Finally, 15 studies from 12 countries were included in this study, and will henceforth be referred to as "contributing studies" in this paper.

In addition to the selected eligible studies mentioned above, the HELIX project's subcohorts EDEN (France), INMA (Spain), and MoBa (Norway), were not eligible for the present study as the recruitment of their respective participants took place before 2007, or only in part after 2007 and did not have enough subsamples of pregnant women or had few individuals with BPA measured (Guxens et al., 2012; Vrijheid et al., 2014; Heude et al., 2016; Magnus et al., 2016; Haug et al., 2018; Maitre et al., 2018). The French survey ESTEBAN was not included in the present study because the related French data on BPA exposure (Fillol et al., 2021) were not yet available at the time the data sharing agreements were drawn up.

All contributing data providers have signed a Joint Data Controller agreement developed under HBM4EU, setting out the general framework of the data sharing and analysis, in compliance with the European Union's General Data Protection Regulation (GDPR) (Regulation 2016/679) (https://gdpr.eu/). The Flemish Institute for Technological Research (*VITO*) developed the global framework of the Joint Data Controller agreement. *VITO* also ensured that all ethics approvals were valid and in place for the present BPA Study, as required for all existing data collection-based studies under HBM4EU (Knudsen et al., 2022).

2.4. Characteristics of the contributing studies

The general characteristics of the 15 studies with existing HBM data on BPA included in the present study are provided in Table 1. The description was based on information available through the IPCHEM Portal (https://ipchem.jrc.ec.europa.eu/#discovery) and from the data owners. Detailed descriptions of each of the original HBM data used in this study are presented in **Supplementary Material S2**.

Of the 15 studies included in this study, nine were from three previous major projects that had already undergone harmonized study protocols (including Quality assurance/Quality control of BPA analysis) or international collaborations: six DEMOCOPHES studies from Belgium, Denmark, Spain, Luxembourg, Sweden, and Slovenia; two studies from the Helix project from Greece (HELIX-RHEA) and the United Kingdom (HELIX-BIB); and one study was the ELFE survey (France). Three European sub-regions, as predefined under HBM4EU (Gilles et al., 2021), were covered by 14 of the contributing studies: Northern Europe (4 studies: HELIX-BIB, OCC, and DEMOCOPHES Denmark and Sweden), Western Europe (7 studies: 3xG, ELFE, ESB, FLEHS III, PBAT, and DEMOCOPHES Belgium and Luxembourg) and Southern Europe (3 studies: HELIX-RHEA, and DEMOCOPHES Slovenia and Spain). The study from Israel (IBS) was classified as "Outside Europe". No study was identified from Eastern Europe.

The contributing studies were mostly cross-sectional studies, and a few others were longitudinal surveys (cohort studies: 3xG, ELFE, HELIX studies, and OCC). Because of the non-inclusion of six studies initially identified at the stage of the inventory of existing studies with available BPA data, which covered the period from 2007 to 2018, the data collection period for all contributing studies was set between 2007 and 2014. The target populations for the 3xG, ELFE, OCC and HELIX studies were pregnant women, the target populations for the ESB, IBS, FLEHS III and PBAT studies were the general population, and the remaining studies were targeted at mother–child pairs from the general population (DEMOCOPHES). The coverage area of population samplings were mainly at the national or regional level. However, 3xG, ESB and HELIX-BIB studies focused only at the local level (communities, cities). In all contributing studies, additional information about participants, in particular individual characteristics or environmental exposure parameters, was collected using standardized questionnaires.

For the measurement of biomarkers, first-morning urine and spot urine samples were collected from 53 % (8/15) and 40 % (6/15) of original studies, respectively. Only the German Environmental Specimen Bank (ESB) collected 24-hour urine samples. BPA concentrations were measured in the collected urine samples using various mass spectrometry methods: gas chromatography–mass spectrometry (GC–MS), gas chromatography coupled to tandem mass spectrometry (GC–MS/MS), gas chromatography in combination with electron capture negative ion mass spectrometry (GC-ECNI/MS), liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS), and HPLC-MS/MS with online or presenting solid phase extraction (SPE) purification after deconjugation and isotope dilution. The laboratories that performed BPA analyses were specific to each of the contributing studies. For some studies, the BPA measurements were performed only on a specific sub-sample of the total recruited population (ELFE, HELIX-BIB, and HELIX-RHEA cohorts).

2.5. Post-harmonization process and collection of the selected variables

About one hundred variables were requested from each participating study. The variables of interest were identified through of an in-depth review of the literature carried out as part of the HBM4EU activities (HBM4EU, 2022a; b). The information collected covered sampling and analytical parameters, physiological, anthropometric and sociodemographic characteristics, and BPA exposure determinants. Data collected were all harmonized prior to the data sharing process between the study data owners and the receiving data controller (*Santé publique France,* the French Public Health Agency). A specific codebook for the present BPA Study was developed by *ISGlobal* (the Barcelona Institute for Global Health) under HBM4EU, and was sent by *Santé publique France* to each data owner of the selected studies. Thus, in the end, all the variables requested were assumed to have been collected in the same format in terms of the nature of the variables, their units and modalities. Details about the post-harmonization procedures in HBM4EU can be found in Gilles et al. (Gilles et al., 2021). Each data provider was asked to select eligible participants based on four main parameters (labeled "filtering variables"): BPA measurement in urine, sampling period between 2007 and 2018, females only, and adults aged 18 and over. Therefore, for the five collected variables: "bpa_concentration", "matrix", "samplingyear", "sex" and "ageyears", there were no possible missing data in the shared datasets.

Overall, the following variables were harmonized for the present BPA Study: i) identifying participant variables: identifier (ID) of the participant; ID participant of participant (main study participant) to which this participant is linked; ID of the group (*e.g.,* from a repeated measures design study); ii) filtering variable: matrix of the sample; year of sample collection; sex of participant; age in years of the participant at sampling; iii) BPA data: total BPA level measured in the sample (μg/L); limit of detection (LOD) and limit of quantification (LOQ) of total BPA associated with the measurement of the sample (μg/L); free BPA (unconjugated) level measured in the sample (μg/L); LOD and LOQ of free BPA associated with the measurement of the sample (μg/L); conjugated BPA level measured in the sample (μg/L); LOD and LOQ of conjugated BPA associated with the measurement of the sample (μg/L); iv) sampling variables: ID of the biological sample; laboratory in which samples were analyzed (abbreviation name); name of analytical method used; type of tube used for sample and storage; number of samples for one individual; month of sample collection; time of day of sample; urine volume collected; concentration of creatinine in urine of the sample (g/L); specific gravity of urine of the sample; v) participant sampling characteristics: whether or not the participant belongs to general population (study design); gestational status of the participant at sampling; gestational weeks of the mother at sample taken; country of birth; weight of the participant at sampling (kg); height of the participant at sampling (cm); level of education at sampling (ISCED); socioeconomic status (SES) of the participant at sampling; current labor status (occupation status); industrial sectors of occupation (occupation); country of

residence of the participant at sampling (ISO 3166–1 alpha-2); NUTS Levels of residence of the participant at sampling (NUTS 2016); subdivision of country of residence of the participant at sampling (ISO 3166–2); degree of urbanization of residence at sampling of the participant; and vi) determinants of exposure: smoking (smoking status of the participant at sampling; number of cigarettes smoked per day; passive exposure to cigarette smoke by the participant at sampling); type of drinking water (tap water, bottled water; water from well source) and frequencies of consumption; certain dietary habits (drinking beverages other than water contained in plastic bottles, consumption of food in contact with plastic packaging; consumption of canned food; consumption of canned drinks) and frequencies; certain domestic or household uses (plastic crockery/dishes; plastic films for food; plastic electric kettles; food mixers; plastic containers for heating foods in microwave; plastic baby bottles (handling)) and frequencies; certain individual characteristics (use of thermal papers; use of plastic medical devices; have a dental sealant; wear contact eye lenses; use of cosmetics and personal care products; wear sport clothes in polyester and/or elastane; wear synthetic clothes; practice of a physical activity) and frequencies; number of daily hours typically spent inside per day; starting year of residence at the current place; presence of plastic flooring in the house.

LOQ was available for all contributing studies; whereas LOD was available for only two-thirds of the contributing studies. Only the ELFE study (France) measured both free and total BPA. None of the contributing studies had measured conjugated BPA. All other studies measured total BPA only. Urinary creatinine was measured in all contributing studies. The specific gravity of urine samples was measured in only one-fifth of the collected studies. Analytical information was available in all data collected regarding the laboratory where the BPA samples were analyzed, the analytical method used for BPA measurement, and the type of tube used for urine collection. For the other variables of interest (**Supplementary Material S3**), most had not been collected in respective studies because they were not planned from the beginning. Finally, no data could be shared for one third of the variables requested due to 100 % of missing data. For the remaining requested variables, data were only available in a few studies. As a result, with the exception of variables covering general information such as the type of population and the country of residence, only data on smoking status and the height of participants were collected in all the studies, with a "missing data" rate per contributing study less than 13 % and 5 %, respectively (Table **S2**).

2.6. Statistical analysis

First, an analysis of the main characteristics of the contributing studies was performed in order to evaluate their similarities and specific features. Afterwards, a descriptive analysis of all individual data collected in the contributing studies was performed (list of variables, rate of missing values) to identify all relevant variables that could be used for statistical analyses.

The sociodemographic characteristics of the study population were described for the total population sample per contributing study. Since only one participating study had data on free BPA and none on conjugated BPA, the analysis ultimately focused only on total BPA measured by all contributing studies. Descriptive statistics of total BPA concentrations in urine were performed for each contributing study. The descriptive information presented was for urinary creatinine levels (geometric mean (GM) with 95 % confidence intervals (95 %CI), percentage of values below 0.3 g/L or above 3 g/L) and for total BPA concentrations (LOQ, quantification rate, GM and 95 %CI, and percentiles). In this study, left-censored data (i.e., chemical levels below the LOD or LOQ) were imputed using multiple imputation by chained equations (Royston, 2014). Urinary concentrations of total BPA were expressed in both μg/L and μg/g creatinine (for participants with available data on urinary creatinine concentration). A comparative description of total urine BPA concentrations between studies was done using box plots and according to three main parameters: population type (pregnant women, and women from the general population), geographic living area (Northern Europe, Western Europe, Southern Europe, and Outside Europe), and relevant age category (20–39 years, and 40–59 years). Minimum and maximum were calculated using the following formula: "values below Q1 − 1.5 IQR" and "values above Q3 + 1.5 IQR", where Q1 and Q3 indicate the first and third quartiles, respectively, and IQR is the interquartile range. Values outside this range were defined as extreme values.

Linear-mixed regression models were used to investigate determinants of urinary BPA concentrations in women from combined studies. Detailed information is given in **Supplementary Material S5**.

All statistical analyses were performed using R 4.1.3 (R Core Team).

3. Results and discussion

3.1. Characteristics of the study population

The population was characterized based on a few selected variables available in almost all contributing studies (Table 2). A total of 4,226 women were included from 15 studies. The rate of missing data was highly variable across studies, ranging from 0 % to 100 % depending on the variable. The total population consisted of 94.7 % women aged 20–49 years (36.8 % were 20–29 years, 45.9 % 30–39 years, and 12.0 % were 40–49 years). Women younger than 20 years and older than 49 years represented only 0.9 % and 4.4 % of the total population, respectively, and came from 7 studies out of the 15 contributing studies. The German ESB study population covered only 20–29 years, whereas the Belgian population from the Flemish study FLEHS III included only participants over 49 years. Body mass index (BMI) was distributed differently among the contributing studies, mainly because the overall study population included both pregnant women and non-pregnant women; this index was not calculated for several participants due to missing height and/or weight data. Four-fifths of the study population (81 %) were non-smokers (self-reported). This high rate of non-smokers is consistent with the fact that the overwhelming majority of the study population were women of childbearing age, including specific populations of pregnant women. However, in all contributing studies for which the information was available, women also reported to be exposed to passive smoking (self-reported), with rates of passive smoking exposure ranging from 26 % in ELFE (France) to 90 % in HELIX-RHEA (Greece).

3.2. Levels of exposure of BPA among women from the contributing studies

3.2.1. Distribution of total urine BPA concentrations

The distributions of total urine BPA concentrations of the contributing studies, raw and creatinine-standardized levels, are presented in Table 3.

The LOQ values from all contributing studies were very similar, ranging from 0.1 to 0.3 μg/L, except for the DEMOCOPHES (Luxembourg) and PBAT (Austria) studies, which were 1.0 μg/L and 2.5 μg/L, respectively. Excluding the DEMOCOPHES Luxembourg, OCC (Denmark) and PBAT (Austria) studies, the proportion of urine samples with quantifiable BPA levels (values ≥ LOQ) ranged from 90 % to 100 %. Total BPA was quantified in 85 % and 46 % of urine samples of women from the OCC (Denmark) and the DEMOCOPHES Luxembourg, respectively, but only in 4 % of those from the PBAT (Austria). The high rate of non-detected BPA from the PBAT study can be explained by its detection limit (2.5 μg/L), which was 25 times higher than that of the other contributing studies.

The lowest GM concentration of total BPA was observed in the ELFE study (0.77 μg/L) and the highest GM was observed in both the DEMOCOPHES Belgium and HELIX-RHEA studies (2.47 μg/L). The highest 95th percentile values were observed in the HELIX-BIB and IBS

Table 2
Overall characteristics of the 4226 women included in the BPA Study (this study) from the 15 eligible studies.

Characteristics	N (%)	Number of participants per data collection, n (%)														
		3xG (Belgium)	DEMOC* (Belgium)	DEMOC* (Denmark)	DEMOC* (Spain)	DEMOC* (Luxembourg)	DEMOC* (Sweden)	DEMOC* (Slovenia)	ELFE (France)	ESB (Germany)	FLEHS III (Belgium)	HELIX BIB (UK)	HELIX RHEA (Greece)	IBS (Israel)	OCC (Denmark)	PBAT (Austria)
Total of participants	4226 (100)	150 (100)	129 (100)	145 (100)	115 (100)	60 (100)	98 (100)	107 (100)	1741 (100)	60 (100)	101 (100)	205 (100)	194 (100)	117 (100)	842 (100)	162 (100)
Sampling year																
2007	277 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	109 (53.2)	168 (86.6)	0 (0)	0 (0)	0 (0)
2008	152 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	30 (50)	0 (0)	96 (46.8)	26 (13.4)	0 (0)	0 (0)	0 (0)
2009	30 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	30 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2010	131 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (0.9)	123 (75.9)
2011	2969 (70.3)	72 (48.0)	86 (66.7)	145 (100)	105 (91.3)	59 (98.3)	39 (39.8)	70 (65.4)	1741 (100)	0 (0)	0 (0)	0 (0)	0 (0)	117 (100)	496 (58.9)	39 (24.1)
2012	525 (12.4)	77 (51.3)	43 (33.3)	0 (0)	10 (8.7)	1 (1.7)	59 (60.2)	37 (34.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	298 (35.4)	0 (0)
2013	41 (1.0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	40 (4.8)	0 (0)
2014	101 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	101 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Participants' age (years)																
< 20	40 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (1.2)	0 (0)	0 (0)	10 (4.9)	1 (0.6)	0 (0)	2 (0.3)	7 (4.3)
20–29	1557 (36.8)	67 (44.7)	1 (0.8)	0 (0)	2 (1.7)	0 (0)	3 (3.1)	0 (0)	817 (46.9)	60 (100)	0 (0)	106 (51.7)	74 (38.1)	39 (33.3)	332 (39.4)	56 (34.6)
30–39	1941 (45.9)	82 (54.7)	61 (47.3)	51 (35.2)	40 (34.8)	27 (45.0)	47 (48.0)	55 (51.4)	852 (48.9)	0 (0)	0 (0)	84 (41.0)	111 (57.2)	17 (14.5)	486 (57.7)	28 (17.3)
40–49	504 (12.0)	1 (0.6)	67 (51.9)	89 (61.4)	73 (63.5)	33 (55.0)	48 (48.9)	52 (48.6)	52 (3.0)	0 (0)	0 (0)	5 (2.4)	8 (4.1)	23 (19.7)	22 (2.6)	31 (19.1)
50–59	109 (2.6)	0 (0)	0 (0)	5 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	51 (50.5)	0 (0)	0 (0)	25 (21.4)	0 (0)	28 (17.3)
≥ 60	75 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	50 (49.5)	0 (0)	0 (0)	13 (11.1)	0 (0)	12 (7.4)
Body mass index (BMI, kg/m2)																
BMI<18.5	72 (1.7)	0 (0)	5 (3.9)	6 (4.2)	7 (6.1)	2 (3.3)	2 (2.0)	0 (0)	2 (0.1)	3 (5.0)	4 (4.0)	2 (1.0)	4 (2.1)	6 (5.1)	22 (2.6)	7 (4.3)
18.5 ≥ BMI<25	1725 (40.8)	0 (0)	81 (62.8)	104 (71.7)	68 (59.1)	41 (68.3)	63 (64.3)	72 (67.3)	355 (20.4)	52 (86.7)	47 (46.5)	56 (27.3)	134 (69.1)	54 (46.2)	496 (58.9)	102 (63.0)
25 ≥ BMI<30	1236 (29.3)	0 (0)	28 (21.7)	21 (14.5)	26 (22.6)	11 (18.4)	22 (22.5)	18 (16.8)	691 (39.7)	4 (6.7)	31 (30.7)	74 (36.1)	37 (19.1)	26 (22.2)	218 (25.9)	29 (17.9)
BMI≥30	765 (18.1)	0 (0)	8 (6.2)	13 (8.9)	14 (12.2)	6 (10.0)	9 (9.2)	16 (15.0)	473 (27.2)	1 (1.6)	19 (18.8)	67 (32.7)	17 (8.8)	15 (12.8)	101 (12.0)	6 (3.7)
Missing data [a]	428 (10.1)	150 (100)	7 (5.4)	1 (0.7)	0 (0)	0 (0)	2 (2.0)	1 (0.9)	220 (12.6)	0 (0)	0 (0)	6 (2.9)	2 (0.9)	16 (13.7)	5 (0.6)	18 (11.1)
Pregnancy at sampling time																
No	326 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	60 (100)	0 (0)	105 (98.13)	0 (0)	60 (100)	101 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Yes	3134 (74.2)	150 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.87)	1741 (100)	0 (0)	0 (0)	205 (100)	194 (100)	0 (0)	842 (100)	0 (0)
Missing data [b]	766 (18.1)	0 (0)	129 (100)	145 (100)	115 (100)	0 (0)	98 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	117 (100)	0 (0)	162 (100)
Education (ISCED levels) [c]																
Low education (0–2)	255 (6.0)	4 (2.7)	6 (4.7)	4 (2.7)	43 (37.4)	2 (3.3)	2 (2.0)	12 (11.2)	57 (3.3)	0 (0)	27 (26.7)	84 (41.0)	9 (4.6)	5 (4.3)	0 (0)	0 (0)
Medium education (3–4)	753 (17.8)	35 (23.3)	19 (14.7)	13 (9.0)	29 (25.2)	19 (31.7)	28 (28.6)	43 (40.2)	359 (20.6)	0 (0)	19 (18.8)	33 (16.1)	107 (55.2)	49 (41.9)	0 (0)	0 (0)
High education (>=5)	1956 (46.3)	111 (74.0)	104 (80.6)	127 (87.6)	43 (37.4)	39 (65.0)	67 (68.4)	52 (48.6)	1118 (64.2)	60 (100)	52 (51.5)	64 (31.2)	77 (39.7)	42 (35.9)	0 (0)	0 (0)
Missing data [b]	1262 (29.9)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (1.0)	0 (0)	207 (11.9)	0 (0)	3 (3.0)	24 (11.7)	1 (0.5)	21 (17.9)	842 (100)	162 (100)

(*continued on next page*)

Table 2 (*continued*)

Characteristics	N (%)	Number of participants per data collection, n (%)													
		3xG (Belgium)	DEMOC* (Belgium)	DEMOC* (Denmark)	DEMOC* (Spain)	DEMOC* (Luxembourg)	DEMOC* (Sweden)	DEMOC* (Slovenia)	ELFE (France)	ESB (Germany)	FLEHS III (Belgium)	HELIX BIB (UK)	HELIX RHEA (Greece)	IBS (Israel)	OCC (Denmark)	PBAT (Austria)
Smoking status at sampling time																
Non-smoker	3436 (81.3)	135 (90)	117 (90.7)	131 (90.3)	73 (63.5)	57 (95)	92 (93.9)	94 (87.8)	1246 (71.6)	55 (91.7)	85 (84.2)	169 (82.4)	166 (85.6)	84 (71.79)	812 (96.4)	120 (74.1)
Smoker 1–9 cig/day	311 (7.36)	1 (0.67)	5 (3.9)	6 (4.1)	20 (17.4)	3 (5)	4 (4.1)	5 (4.8)	211 (12.1)	0 (0)	6 (5.9)	12 (5.9)	24 (12.4)	0 (0)	0 (0)	14 (8.6)
Smoker 10–19 cig/day	109 (2.58)	3 (2.0)	6 (4.6)	5 (3.5)	12 (10.4)	0 (0)	0 (0)	7 (6.5)	56 (3.2)	0 (0)	4 (4.0)	0 (0)	3 (1.5)	0 (0)	0 (0)	13 (8.0)
Smoker >=20 cig/day	46 (1.09)	11 (7.33)	1 (0.8)	3 (2.1)	9 (7.8)	0 (0)	0 (0)	1 (0.9)	6 (0.3)	0 (0)	2 (2.0)	0 (0)	1 (0.5)	0 (0)	0 (0)	12 (7.4)
Missing data [d]	324 (7.67)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	2 (2.04)	0 (0)	222 (12.8)	5 (8.3)	4 (4.0)	24 (11.7)	0 (0)	33 (28.2)	30 (3.6)	3 (1.9)
Passive smoking exposure [e]																
No	1691 (40.0)	85 (56.7)	48 (37.2)	25 (17.2)	29 (25.2)	27 (45.0)	48 (48.9)	78 (72.9)	1058 (60.8)	43 (71.7)	46 (45.5)	145 (70.7)	19 (9.8)	40 (33.9)	0 (0)	0 (0)
Yes	1229 (29.1)	65 (43.3)	79 (61.2)	111 (76.6)	86 (74.8)	33 (55.0)	48 (48.9)	29 (27.1)	451 (25.9)	17 (28.3)	34 (33.7)	56 (27.3)	175 (90.2)	45 (38.1)	0 (0)	0 (0)
Missing data [b]	1306 (30.9)	0 (0)	2 (1.55)	9 (6.21)	0 (0)	0 (0)	2 (2.04)	0 (0)	232 (13.3)	0 (0)	21 (20.8)	4 (1.95)	0 (0)	32 (28.2)	842 (100)	162 (100)

*DEMOC = DEMOCOPHES.

[a] Missing values was related to the height and/or weight of the participant.

[b] Missing data or data not applicable (variable not existing from the original study protocol).

[c] ISCED: International Standard Classification of Education.

[d] Missing data or data available only for smokers (smokers from studies without data collection about the number of cigarettes smoked).

[e] Exposure to passive smoking at home or in the workplace (usual exposure status at sampling time).

Table 3
Total urine BPA concentrations per study collection, raw (μg/L) and creatinine-standardized (μg/g creatinine) levels.

Study [a]	Country	n	Unit	LOQ [b]	QF (%) [c]	GM	[95 %CI] [d]	Percentiles						
								P10	P25	P50	P75	P90	P95	P99
3xG_BE	Belgium	150	μg/L	0.2	100	1.27	[1.12–1.44]	0.43	0.79	1.22	2.10	3.09	4.60	7.34
		150	μg/g creatinine			1.59	[1.41–1.79]	0.69	0.94	1.34	2.45	3.93	4.88	12.3
DEMOCOPHES_BE	Belgium	129	μg/L	0.2	100	2.47	[2.08–2.93]	0.86	1.37	2.28	3.72	7.26	11.6	43.1
		129	μg/g creatinine			2.26	[1.93–2.65]	0.95	1.31	2.07	3.14	5.76	9.06	48.9
DEMOCOPHES_DK	Denmark	145	μg/L	0.3	100	2.12	[1.77–2.53]	0.42	0.99	2.05	4.00	8.14	11.4	37.8
		145	μg/g creatinine			2.20	[1.88–2.58]	0.58	1.18	2.10	3.97	6.88	8.96	27.7
DEMOCOPHES_ES	Spain	115	μg/L	0.2	100	2.02	[1.63–2.50]	0.39	0.91	2.22	4.73	8.41	11.8	17.8
		115	μg/g creatinine			2.02	[1.68–2.42]	0.48	1.06	2.09	3.82	6.15	8.83	10.6
DEMOCOPHES_LU	Luxembourg	60	μg/L	1	100	1.73	[1.45–2.06]	< LOQ	< LOQ	< LOQ	2.85	5.26	6.56	8.41
		58 [e]	μg/L	1	100	1.71	[1.43–2.04]	< LOQ	< LOQ	< LOQ	2.80	5.36	6.69	8.48
		58 [e]	μg/g creatinine			1.84	[1.56–2.18]	_	_	_	2.74	4.93	5.93	6.84
DEMOCOPHES_SE	Sweden	98	μg/L	0.1	100	1.24	[1.06–1.46]	0.43	0.72	1.27	2.10	3.41	4.98	6.19
		98	μg/g creatinine			1.21	[1.06–1.38]	0.54	0.73	1.11	1.85	2.75	3.18	4.92
DEMOCOPHES_SI	Slovenia	107	μg/L	0.1	100	1.50	[1.12–2.01]	0.10	0.49	1.97	4.00	7.99	13.0	40.5
		107	μg/g creatinine			1.14	[0.86–1.50]	0.09	0.46	1.58	2.57	6.21	9.33	25.1
ELFE_FR	France	1741	μg/L	0.3	90.5	0.77	[0.73–0.81]	0.11	0.28	0.73	1.65	3.22	5.01	18.7
		1741	μg/g creatinine			0.98	[0.94–1.03]	0.29	0.49	0.94	1.78	3.42	6.15	19.8
ESB_DE [f]	Germany	60	μg/L	0.1	100	1.15	[0.90–1.45]	0.35	0.55	1.21	2.05	3.36	4.28	11.7
		60	μg/g creatinine			1.85	[1.51–2.28]	0.73	0.97	1.71	2.33	4.67	6.38	23.9
FLEHS III_BE	Belgium	101	μg/L	0.2	100	0.96	[0.81–1.15]	0.30	0.51	0.87	1.83	2.90	3.92	10.6
		101	μg/g creatinine			1.85	[1.61–2.13]	0.80	1.16	1.70	3.01	4.37	6.06	11.1
HELIXBIB_UK	United Kingdom	205	μg/L	0.1	100	1.63	[1.44–1.84]	0.53	0.90	1.54	2.96	4.79	6.67	19.8
		205	μg/g creatinine			1.76	[1.59–1.96]	0.72	1.04	1.60	2.75	4.45	6.21	15.2
HELIXRHEA_EL	Greece	194	μg/L	0.1	100	2.47	[2.08–2.92]	0.59	1.09	2.39	4.21	12.1	27.9	53.4
		194	μg/g creatinine			2.44	[2.09–2.84]	0.72	1.27	1.93	3.98	11.69	20.7	48.0
IBS_IL	Israel	117	μg/L	0.3	91.5	2.38	[1.84–3.08]	0.33	1.28	2.67	6.37	11.4	18.5	36.8
		117	μg/g creatinine			2.06	[1.60–2.65]	0.30	1.01	2.21	4.83	9.06	15.9	64.5
OCC_DK	Denmark	842	μg/L	0.12	84.7	0.90	[0.82–0.99]	< LOQ	0.42	1.22	2.32	4.30	6.80	13.4
		838 [g]	μg/L	0.12	85.0	0.90	[0.82–0.99]	< LOQ	0.42	1.22	2.32	4.30	6.80	13.4
		838 [g]	μg/g creatinine			1.03	[0.94–1.12]	_	0.51	1.22	2.39	4.03	6.27	16.6
PBAT_AT [h]	Austria	162	μg/L	2.5	4.32	_	_	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	8.99
		162	μg/g creatinine			_	_	_	_	_	_	_	_	10.9

[a] In all the contributing studies, BPA was measured in spot-urine or in morning-urine samples, except in the German ESB where BPA was measured as 24-h urine collection. Urine concentration parameters were as follows for each study [geometric mean in g/L (and its 95 % confident interval); percentage of values below 0.3 g/L; and percentage of values above 3.0 g/L]: 3xG [0.80 (0.74 – 0.86); 1.33; and 0]; DEMOCOPHES Belgium [1.09 (1.00 – 1.19); 2.33; and 0.78]; DEMOCOPHES Denmark [0.96 (0.89 – 1.04); 1.38; and 0]; DEMOCOPHES Spain [1.00 (0.90 – 1.11); 1.74; and 0]; DEMOCOPHES Luxembourg [0.93 (0.82 – 1.05); 1.72; and 1.72; similar percentages]; DEMOCOPHES Sweden [1.03 (0.93 – 1.13); 2.04; and 0]; DEMOCOPHES Slovenia [1.32 (1.20 – 1.45); 0; and 0.93]; ELFE France [0.78 (0.76 – 0.80); 7.12; and 0.57]; ESB Germany [0.62 (0.54 – 0.70); 6.67; and 0.93]; FLEHS III Belgium [0.52 (0.45 – 0.60); 21.78; and 0.99]; HELIX-BIB United Kingdom [0.92 (0.85 – 1.01); 5.37; and 1.46]; HELIX-RHEA Greece [1.01 (0.91 – 1.12]; 9.28; and 2.06]; IBS Israel [1.16 (1.04 – 1.29]; 1.71; and 0]; OCC Denmark [0.88 (0.84 – 0.92]; 7.76; and 0.60]; and PBAT Austria [1.03 (0.92 – 1.16]; 5.56; and 3.70], respectively.

[b] Limit of quantification (LOQ).

[c] Quantification frequency (QF) or percentage of values > LOQ.

[d] Geometric mean (GM) and its 95% confident interval (95%CI).

[e] Only the participants with available urinary creatinine measurement.

[f] BPA concentrations measured in 24-h urine.

[g] Only the participants with available urinary creatinine measurement.

[h] In the PBAT_AT, almost all percentiles of the BPA distribution were below the LOQ of 2.5 μg/L. The P90 and P95 were respectively 1.35 μg/L (3.85 μg/g creatinine) and 2.36 μg/L (5.37 μg/g creatinine).

studies, 27.9 μg/L and 18.5 μg/L, respectively. In contrast, the lowest 95th percentile values were observed in the FLEHS III study at 3.92 μg/L. Overall, the percentiles of the distribution of unadjusted BPA levels (μg/L) were roughly similar between: 4 DEMOCOPHES studies from Belgium, Denmark, Spain and Slovenia; between 3xG-Belgium, ESB-Germany, and DEMOCOPHES-Slovenia; and between HELIX-BIB (United Kingdom), OCC-Denmark and DEMOCOPHES-Luxembourg.

In total, only six women had no urine creatinine values available (two from DEMOCOPHES-Luxembourg and four from OCC-Denmark). The GM of urinary creatinine ranged from 0.60 g/L in the FLESHIII study to 1.45 g/L in the DEMOCOPHES-Slovenia study. The discrepancy between the GM of urinary BPA concentrations expressed in μg/g creatinine and initially in μg/L was greater in FLEHS III and DEMOCOPHES-Slovenia studies, but in opposite directions: 1.85 μg/g creatinine *vs*. 0.96 μg/L and 1.14 μg/g creatinine *vs*. 1.50 μg/L, respectively. In contrast, this difference was relatively low in the majority of the contributing studies, and did not change the ranking of the data collections with the highest and lowest GMs of urinary BPA concentrations (ELFE and HELIX-RHEA/DEMOCOPHES-Belgium, respectively). All these differences in the impact of adjustment on urinary creatinine can be explained by the initial variability in the distribution of creatinine levels in the respective targeted populations.

3.2.2. *Comparison of total urine BPA levels over population groups*

Figs. 1a,b and 2a,b show the distribution of total urine BPA concentrations from the contributing studies sorted by population type (general population and pregnant women) and by geographic living area (northern, western, southern, and outside Europe), respectively.

For each figure, both unstandardized and creatinine-standardized BPA levels are presented. However, the comparative descriptions of median BPA levels in the present section have focused on raw values only, as the influence of creatinine adjustment can vary greatly from one original contributing study to another (see above, Section 3.2.1), depending on the level and distribution of urine creatinine in each of the original populations. Creatinine standardization itself may be an important contributor to the discrepancies in some biomarker levels observed between different populations or subpopulations (Garde et al., 2004; Nisse et al., 2017).

Boxplots of the Austrian PBAT (Western Europe) were not shown due to the high rate of non-quantified urinary BPA in the PBAT study (95.7 % < LOQ; LOQ=2.5 μg/L). The Austrian PBAT data clearly demonstrate the importance of using sensitive analytical methods (*e.g.*, a low LOD/LOQ) for HBM studies to provide actionable measures of population exposure. This will be even more important in the future, given the observed downward trend in BPA exposure levels (Rodriguez Martin et al., 2023).

The IBS study (Outside Europe) conducted in the general population sampled during 2011 showed higher total BPA distribution parameters (median, and upper percentiles) in Israeli women than those observed in the general population in women from the Flemish Belgian FLEHS III study (Western Europe) sampled in 2014 and in women from the German ESB study (Western Europe) sampled in 2008–2009 (Fig. 1a and Fig. 2a). In addition, Israeli women had the highest median of total BPA concentrations compared to the participating European studies over the 2007–2014 sampling period (Fig. 1a). From the DEMOCOPHES studies conducted in 2011–2012 in general population, women from Luxembourg (Western Europe) presented a lower median value of total BPA than that observed among women from the 5 other countries: Belgium (Western Europe), Slovenia and Spain (Southern Europe), and Denmark and Sweden (Northern Europe) (Fig. 1a and Fig. 2a).

For studies on pregnant women (Fig. 1a), the Greek study HELIX-RHEA (Southern Europe) had the highest distribution values of total BPA compared to the 4 other studies. The HELIX-RHEA women were also from the oldest sampling, covering the period 2007–2008. In contrast, French pregnant women from the ELFE study (Western Europe) sampled during 2011, showed the lowest median total BPA value compared to the 4 other populations of pregnant women from the North, South and Western Europe. Pregnant women from the Danish OCC study (Northern region) and from the Belgian 3xG study (Western Europe), both sampled over the same period 2010–2013, showed similar total BPA medians. This is an

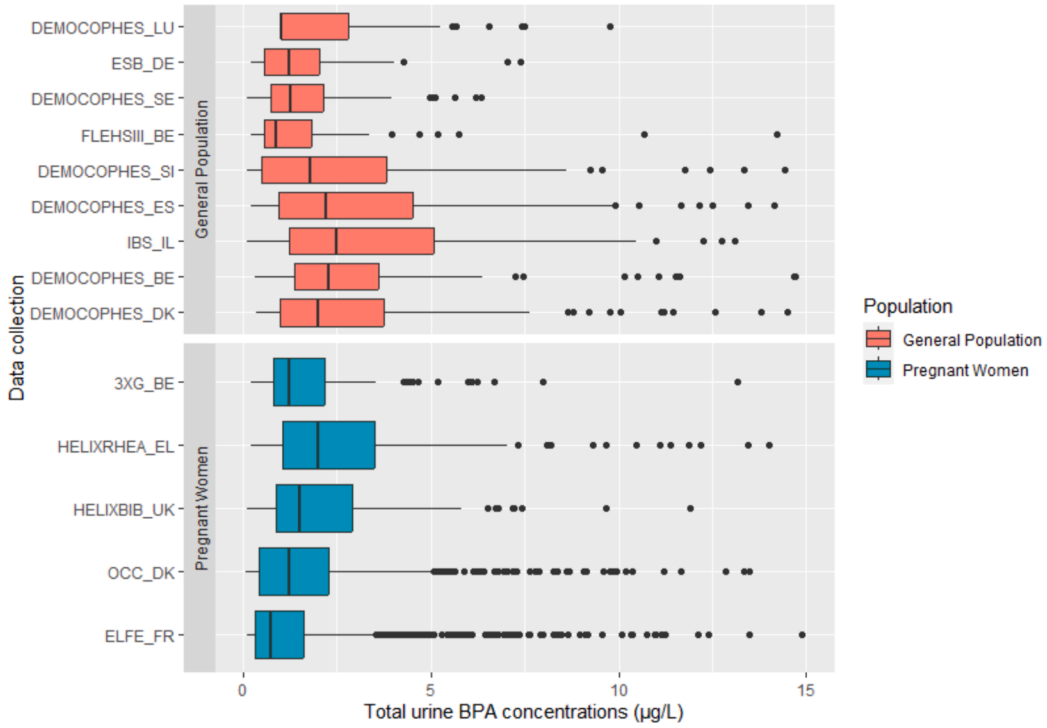

Fig. 1a. Comparative boxplots of the urinary distribution of raw total BPA concentrations (μg/L) from the contributing studies by population type. *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 *μg/L in order to better display the box plots from the various contributing studies.*

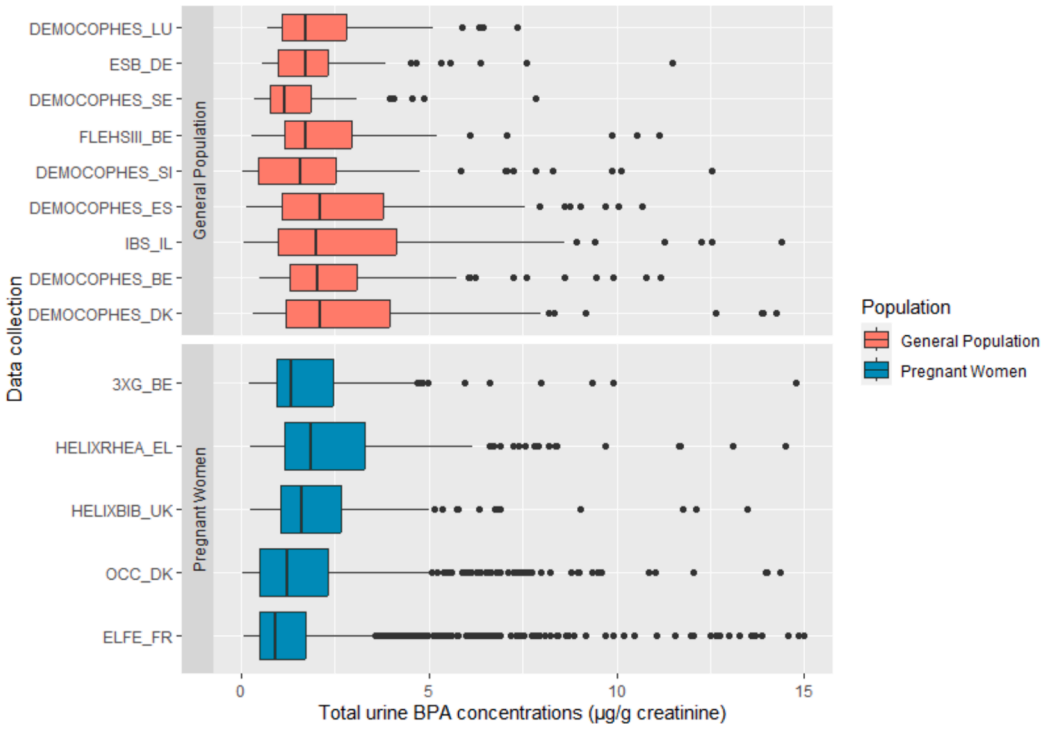

Fig. 1b. Comparative boxplots of the urinary distribution of creatinine-standardized total BPA concentrations (µg/g creatinine) from the contributing studies by population type. *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 µg/g creatinine *in order to better display the box plots from the various contributing studies.*

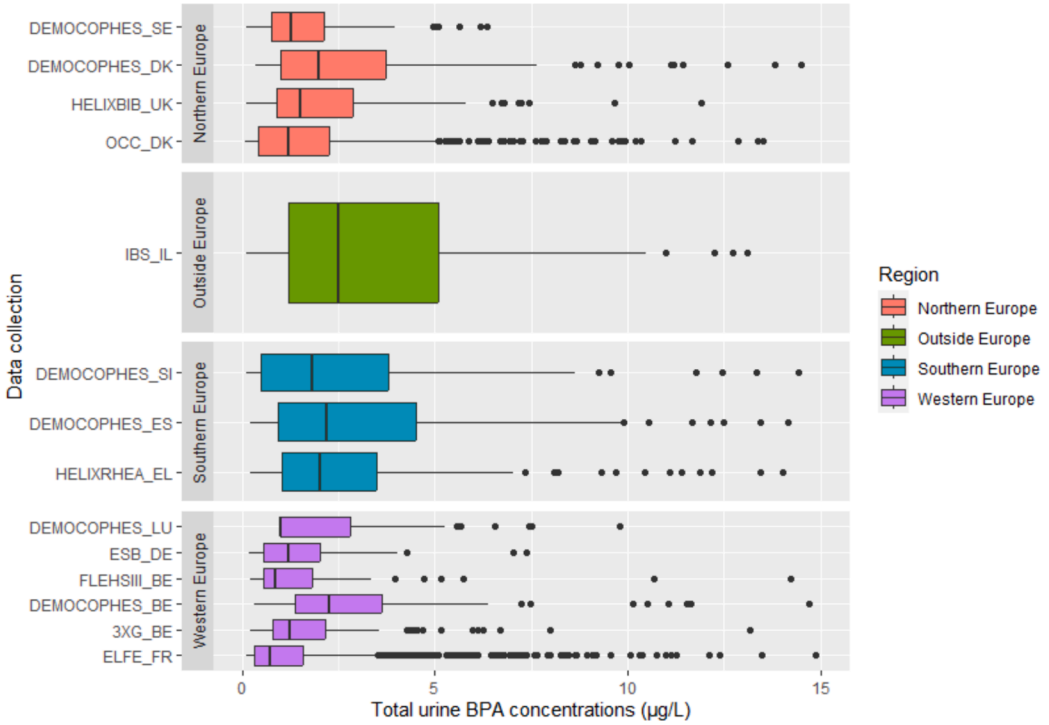

Fig. 2a. Comparative boxplots of the urinary distribution of raw total BPA concentrations (µg/L) from the contributing studies by geographic living area (region). *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 µg/L *in order to better display the box plots from the various contributing studies.*

indication of a potential temporal decreasing trend in BPA levels in pregnant women in Europe, which need to be confirmed by specific temporal trend studies, as the present study does not cover a large number of time points per contributing study over time for further analysis.

3.2.3. Comparison of total urine BPA levels based on individual characteristics

Figs. 3a and 3b compare the total BPA concentrations from the contributing studies depending on the type of population and the age

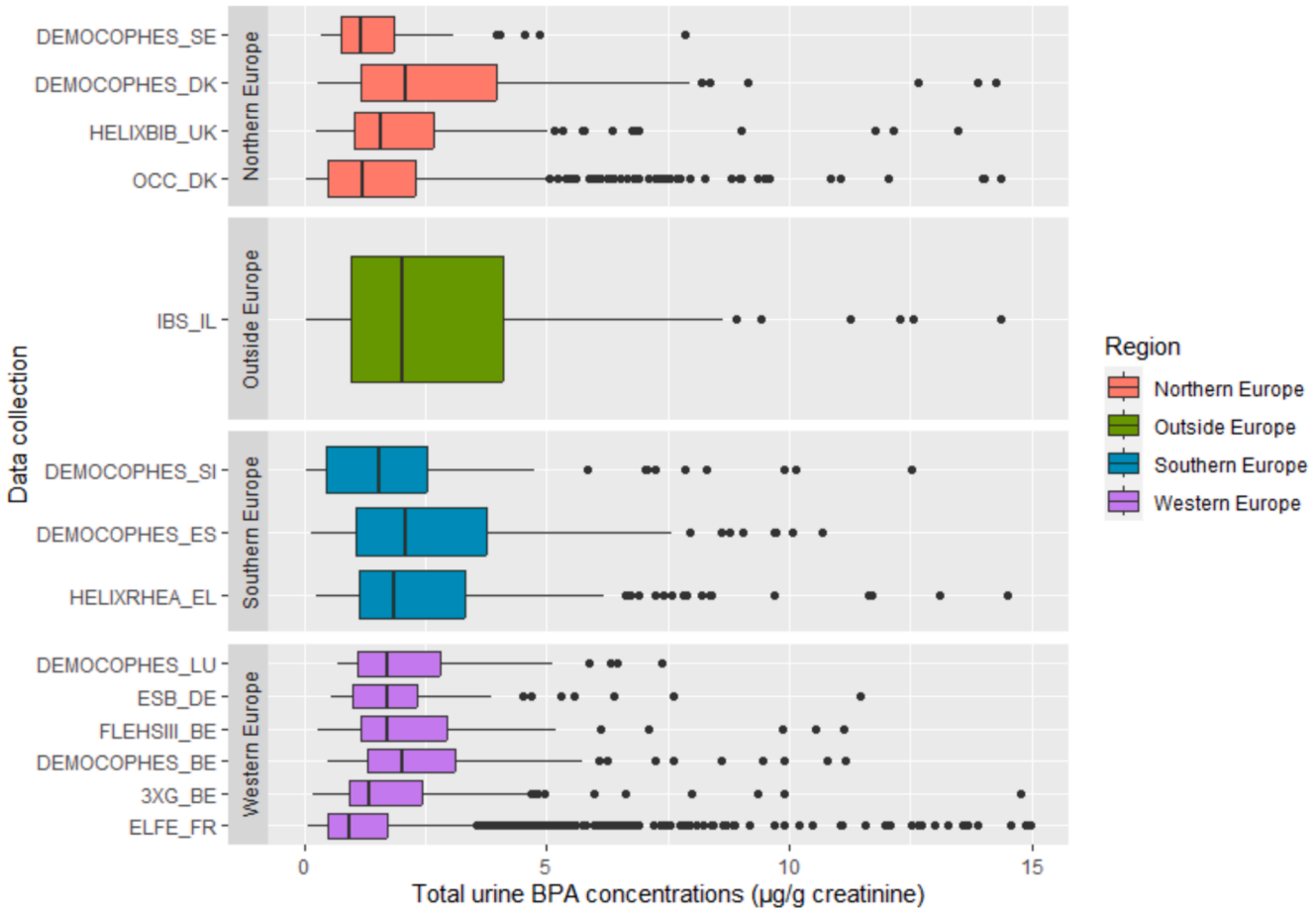

Fig. 2b. Comparative boxplots of the urinary distribution of creatinine-standardized total BPA concentrations (µg/g creatinine) from the contributing studies by geographic living area (region). *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 µg/g creatinine *in order to better display the box plots from the various contributing studies.*

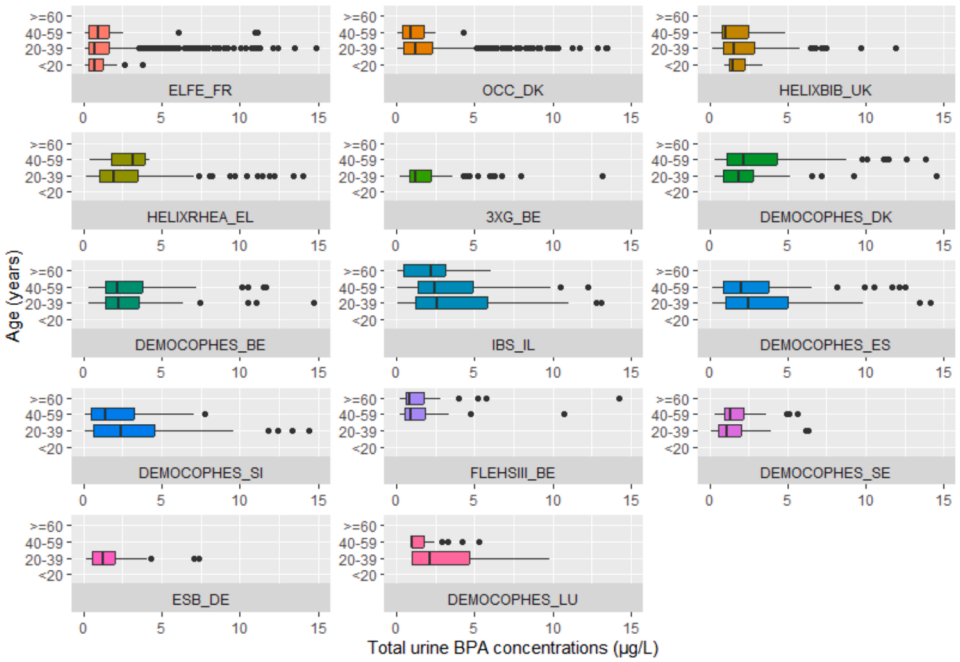

Fig. 3a. Comparative boxplots of the distribution of raw total urine BPA concentrations (µg/L) from the contributing studies by age category. *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 µg/L *in order to better display the box plots from the various contributing studies.*

category. As with the overall description of the BPA medians across the contributing studies (see above, Section 3.2.2), the following descriptions have focused primarily on the raw values (Fig. 3a).

In the general population, the median values of total urinary BPA concentrations were similar between Israeli women aged 20–39-year-old and 40–59-year-old. German ESB had women only from one age category, 20–39 years. Regarding the DEMOCOPHES studies, the difference in the median of total urine BPA concentrations between the two-selected age categories (20–39 years and 40–59 years) was greater in Luxembourg and Slovenian women. Median values in these two countries, as well as among Spanish women, were higher among 20–39-year-olds compared to 40–59-year-olds. In Belgian women, median total urinary BPA concentrations were similar between the two selected age categories, although slightly higher in those aged 20–39 years. In contrast, median values of urinary concentrations of total BPA were higher in both Danish and Swedish women aged 40–59-year-old than those aged 20–39-year-old, but with smaller differences between the two selected age categories.

French pregnant women (ELFE study) aged 20–39-year-old had a slightly higher median value of total BPA concentrations than those aged 40–59-year-old; whereas the opposite comparison was observed in Danish pregnant women (OCC). In the HELIX studies, the number of pregnant women distributed between the two selected age categories did not allow relevant comparisons of the median values of total BPA concentrations; in particular, for women aged 40–59 years, n = 8 in HELIX-RHEA and n = 5 in HELIX-BIB.

Distributions of total urine BPA based on sociodemographic characteristics (BMI, Fig. S2; education, Fig. S3; smoking status, Fig. S5; smoking habit, Fig. S6; and passive smoking exposure, Fig. S4) and sampling year (Fig. S7) are presented in **Supplementary Material S4**. Overall, similar to age (see above), there were no homogeneous trends in the distribution of total BPA levels across the contributing studies, including the DEMOCOPHES studies. Moreover, descriptive comparisons with combined data would have been meaningless due to intrinsic differences between the participating studies, without adjustment for various confounding factors. With regard to the variable sampling year (Fig. S7), although the studies collectively encompass a broad temporal range, the majority of contributing studies each primarily cover only one or two years. As a result, it is not possible to make relevant intra-study comparisons based on sampling year (aimed at identifying time trends).

It should be noted that, in contrast to an inter-study comparison of exposure levels based on raw BPA concentrations (see above, Section 3.2.2), intra-study comparisons of exposure levels based on explanatory variables with standardized BPA levels may generally be more appropriate. In the latter case, the population subgroups being compared are more homogeneous in terms of creatinine-normalized BPA distributions, as the individuals being compared belong to similar demographic groups within the contributing study.

3.3. Comparison of total urine BPA levels with BPA health-based guidance values

To assess whether the levels of BPA measured in the urine of European residents are of concern, health-based guidance values called human biomonitoring guidance values (HBM-GVs) were developed under HBM4EU. A HBM-GV derived for the general population (HBM-GV_{GenPop}) represents the concentration of a substance or its specific metabolite(s) in human biological media (*e.g.*, urine, blood, hair) at and below which, according to current knowledge, there is no risk of health impairment anticipated, and consequently no need for action (Apel et al., 2020). A HBM-GV_{GenPop} of 230 µg total BPA/L urine was initially derived based on the TDI of 4 µg/kg/day for BPA (EFSA, 2015; Ougier et al., 2021b; Lobo Vicente et al., 2023). In this study, no women was above 230 µg total BPA/L urine. In 2023, EFSA re-evaluation drastically lowered the TDI of BPA from 4 to 0.0002 µg/kg/day based in particular on immunological effects (EFSA, 2023). The new EFSA TDI of 0.2 ng/kg bw/day translated into a HBM-GV_{GenPop} of 11.5 ng total BPA/L urine for adults (EEA, 2023). As a result, with the exception of the Austrian PBAT study (where the LOQ was very high), 100 % of women in 14 out of 15 data collections in the present study exceeded the HBM-GV_{GenPop} of 0.0115 µg total BPA/L urine. In the latter configuration, risk characterization ratios (RCRs), previously below 1 for all contributing studies, now range from 341 to 2426 for all contributing studies (Table 4). RCRs are calculated by comparing the 95th percentile of the levels of biomarker measured to the HBM-GV derived, following the equation: $RCR = P95_{biomarker}$ / HBM-GV. If the RCRs are lower than 1, the risk due

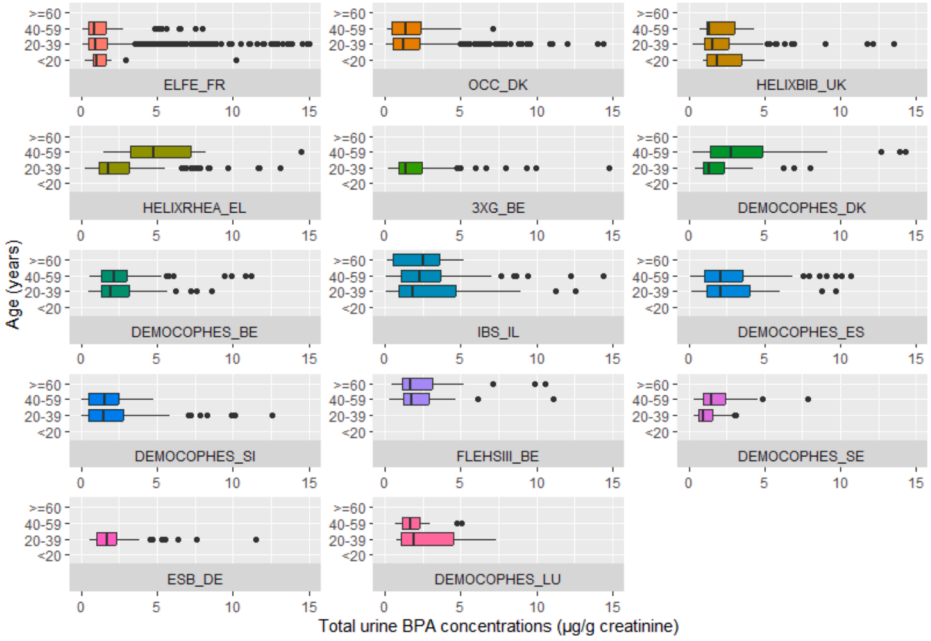

Fig. 3b. Comparative boxplots of the distribution of creatinine-standardized total BPA concentrations (µg/g creatinine) from the contributing studies by age category. *The dots correspond to the scattered values of the BPA distribution. The BPA distributions were restricted to* 15 µg/g creatinine *in order to better display the box plots from the various contributing studies.*

to BPA exposure can be ruled out for the sampled population according to the HBM-GV derived. Conversely, if RCRs are higher than 1, the risk cannot be ruled out for the health of the sampled population and investigations and/or management measures are required (Meslin et al., 2022). It is worth noting a marked downward trend in BPA exposure levels observed in several studies over the past few decades, *e.g.*, in Sweden from 2009 to 2014 (Gyllenhammar et al., 2017), in Denmark from 2009 to 2017 (Frederiksen et al., 2020), in US from 2003 to 2014 (NHANES) (CDC, 2019), and in Canada from 2007 to 2019 (Health Canada, 2021). In the European Union, the population with the highest levels of BPA exposure (here, the 90th percentile) showed a clear decreasing pattern for urinary BPA levels from 2015 (Rodriguez Martin et al., 2023). Consequently, the RCRs calculated in this study should be considered with caution, as they may overestimate the risk for the current population of women in Europe.

3.4. Challenges and perspectives

The objective of the present BPA Study was to describe and compare BPA exposure levels of European women beyond the last decade based on existing HBM data utilizing a larger sample of participants. A second objective was to investigate the determinants of BPA exposure in the resulting study population.

The collection of original data at the individual level from each of the contributing studies allowed us to perform comparative analyses using the same approach for all the included studies, even though statistics were conducted per contributing study. This avoided some of the analytical limitations that would have been generated by collecting aggregated data from eligible studies. However, despite the collection of individual data, a combined analysis of the data collected for the production of single European-wide exposure indicators was ultimately not relevant here due to the heterogeneity of several sociodemographic characteristics across the contributing studies. As a matter of fact, studies can widely differ depending on the target population or biomarkers of interest, which requires the identification of inclusion criteria to create a homogeneous subset of studies prior to a potential combined analysis or even pooled analysis (Bravata and Olkin, 2001; Taioli and Bonassi, 2003). Thus, in addition to controlling for obvious covariates such as sex, age, country, etc., analysts should consider the potential effects of study quality, study size, sampling method and other differences in research protocols of the included studies (Bravata and Olkin, 2001).

Overall, producing HBM data that can be combined from multiple studies from different countries is an important challenge for subsequent analyses and interpretation. This has already been extensively discussed elsewhere as part of the work carried out within HBM4EU (Gilles et al., 2021; Virgolino et al., 2021; Zare Jeddi et al., 2021; Poteser et al., 2022; Fabelova et al., 2023; Pack et al., 2023; Vogel et al., 2023a; Vogel et al., 2023b). However, we will focus here on some of the key parameters regarding the current BPA Study and inherent in the original contributing studies collected: the analytical method applied by the laboratories for the BPA measurement, the types of urine samples collected, the targeted populations, and the content of the study questionnaires.

In our study, both direct (liquid chromatography) and indirect (gas chromatography) methods were used by contributing studies. The different GC or LC methods, sample preparation time for isotope standard addition, and the procedure for deconjugation may partly explain why the French study included and a few other studies included reported lower levels than others. While it has been suggested that the indirect method underestimates total BPA exposure (Gerona et al., 2020), recent opinions indicate that eventual difference in urine BPA concentrations observed with the indirect method and the direct method would not necessarily affect the interpretation of health outcome data (Ashley-Martin et al., 2021). However, such differences in analytical results due

Table 4
Risk Characterization Ratios (RCR) for each contributing study in the BPA Study (this study) calculated using HBM-GV_{GenPop} values derived within HBM4EU.

Study collection [a]	Country	Population	P95 [b] (µg/L)	RCR [c] (calculated using a HBM-GV_{GenPop} of 230 µg total BPA/L urine)	RCR [c] (calculated using a HBM-GV_{GenPop} of 0.0115 µg total BPA/L urine)
3xG_BE	Belgium	Pregnant women (23–40 years old)	4.60	0.02	400
DEMOCOPHES_BE	Belgium	Adult women (27–45 years old)	11.6	0.05	1009
DEMOCOPHES_DK	Denmark	Adult women (31–51 years old)	11.4	0.05	991
DEMOCOPHES_ES	Spain	Adult women (26–48 years old)	11.8	0.05	1026
DEMOCOPHES_LU	Luxembourg	Adult women (33–45 years old)	6.56	0.03	570
DEMOCOPHES_SE	Sweden	Adult women (28–46 years old)	4.98	0.02	433
DEMOCOPHES_SI	Slovenia	Adult women (36–46 years old)	13.0	0.06	1130
ELFE_FR	France	Pregnant women (18–44 years old)	5.01	0.02	436
ESB_DE	Germany	Adult women (20–29 years old)	4.28	0.02	372
FLEHS III_BE	Belgium	Adult women (50–66 years old)	3.92	0.02	341
HELIXBIB_UK	United Kingdom	Pregnant women (18–42 years old)	6.67	0.03	580
HELIXRHEA_EL	Greece	Pregnant women (18–42 years old)	27.9	0.12	2426
IBS_IL	Israel	Adult women (24–73 years old)	18.5	0.08	1609
OCC_DK	Denmark	Pregnant women (19–43 years old)	6.80	0.03	591
PBAT_AT	Austria	Adult women (18–64 years old)	< LOQ	nc	nc

[a] Contributing study to the present BPA Study.
[b] 95th percentile of total urine BPA distribution from the data collection.
[c] Risk Characterization Ratio (RCR). RCRs not calculated (nc) for the PBAT study as its P95 was under the limit of quantification (LOQ).

to the method used are not suitable for producing indicators of exposure levels at a higher scale. Moreover, material and handling of biological specimens may also be external sources of contamination to BPA in the laboratory (Longnecker et al., 2013; Gyllenhammar et al., 2014), which is another parameter that should be controlled to avoid too much variability. It is therefore preferable in the framework of multi-HBM studies, in this case on BPA exposure, that the measurement of chemicals is performed using a standardized method and conducting quality assurance/quality control (QA/QC) programs of the participating laboratories. It is worth noting, however, that a recent *meta*-analysis found no difference in mean urinary BPA concentrations among different analytical techniques used (HPLC-MS, GC–MS, or others) (Colorado-Yohar et al., 2021). BPA was included in the DEMOCOPHES Inter-Laboratory Comparison Investigations and External Quality Assurance Schemes (ICI/EQUAS) and the laboratories that performed the analysis were those that had successfully completed the program (Schindler et al., 2014; Covaci et al., 2015). Several laboratories across EU countries had been approved under HBM4EU for the analysis of BPA biomarkers according to the defined QA/QC schemes (Esteban Lopez et al., 2021; Vaccher et al., 2022). For future HBM studies in Europe, this will contribute to better comparability of results of BPA exposure measurements (Govarts et al., 2023; Vorkamp et al., 2023).

In general, spot urine sampling does not take into account the daily variability of exposure to exogenous substances, compared to the so called golden standard 24-hour urine samples. In practice, the measurement of total urine BPA concentrations in HBM studies is often based on spot samples, often for logistical and cost reasons (Forde et al., 2022). In the present study, only the German ESB data were obtained from 24-hour urine samples. With the exception of the DEMOCOPHES, 3xG, and OCC data, which were based on morning urine samples, all other contributing studies were based on spot urine samples. Spot urine does not take into account the daily variability of exposure either, but it can still bring some information on daily variation at the population level. In a biomonitoring context, the collection of spot samples for the measurement of substances with short elimination half-lives, such as BPA, is a good compromise if the population is large enough and may adequately reflect the global exposure of the population (Ye et al., 2011). Intraclass correlation coefficients from repeated measurements of BPA in urine can vary widely, depending on the sampling time frame and frequency, the total number of collected samples and the applied urinary dilution correction (Roggeman et al., 2022). In terms of accounting for urine dilution, some studies have shown that the creatinine-standardized approach would be more reliable than the specific gravity normalization approach, considering the variability of contaminants in spot urine samples (Mok et al., 2022). However, there is growing evidence that specific gravity would be better than creatinine for the adjustment of non-persistent urinary chemical biomarker data (Carrieri et al., 2000; Kuiper et al., 2021). As in several HBM studies, we presented BPA exposure values both as raw total BPA (μg/L) and standardized for urine creatinine (μg/g creatinine), primarily because urine creatinine was the only parameter accounting for urine dilution that was present in all contributing studies. Nevertheless, this approach is not optimal. The best way to account for exposure variability resulting from urinary dilution should be explored in a substance-by-substance approach and based on substance-specific kinetics. In addition, changes in creatinine metabolism during pregnancy affect urine dilution, which can, likewise in the present study, play a role on the measured BPA value adjusted by creatinine (Braun et al., 2011). In the latter case, the investigation of a relationship between exposure levels and individual characteristics that could also be directly or indirectly related to the level of creatinine excreted should be based on a best-fit method (O'Brien et al., 2017).

HBM surveys are based on study populations, which are recruited in accordance with the purposes of each study. In our study, one of the main barriers to the ability to combine data from the contributing studies is the fact that they involved populations of women sampled in different contexts and for different purposes (pregnant women cohorts, women from the general population). The initial interest in collecting various categories of women was to be able to compare BPA exposure levels both within and between different population types. For example, studies have shown that several sociodemographic characteristics, including gestational factors, are predictive of BPA concentration levels in women (Casas et al., 2013; Arbuckle et al., 2015; Philips et al., 2018). However, this objective could not be fully explored because even within the same population types, the initial inclusion criteria were not necessarily similar. With regard to the present study, it is also important to consider the different sizes of the study samples when interpreting the data, as this may affect the average levels of BPA observed in the different contributing studies. In this instance, the French data represented the largest sample size (two-fifths of the total sample) and also had the lowest mean BPA level among the contributing studies. This crude observation is consistent with the *meta*-analysis conducted by Colorado-Yohar et al. (2021), which found a negative association between mean urinary BPA and study sample size.

Developing questionnaires is a key process in the preparation of HBM studies, and this requires a substantial effort to ensure the adequate collection of the information needed for a proper characterization of the exposure to environmental chemicals (Fiddicke et al., 2021; Gonzalez-Alzaga et al., 2022). Overall, in this study, there was no discernible difference in BPA levels between technical methods (matrix, sampling/storage tube, and laboratory analysis methods) and sociodemographic characteristics (population type, country, and European geographic living area). Furthermore, no variable other than urinary creatinine was significantly associated with BPA levels, in multivariate models examined with the entire combined population. The characterization of BPA exposure determinants among European women was challenging in the present study because of the heterogeneity of the availability of data in existing original BPA studies (**Supplementary Material S3**), which did not allow for a more thorough investigation of the determinants of BPA exposure in the resulting combined population (**Supplementary Material S5**). One third of the requested variables could not be shared as they were not collected in the original study questionnaires, and for several other variables data were available in only a few studies. However, the prior definition of relevant key variables, the "filtering variables", in our inclusion criteria allowed us to minimize the presence of missing data for a few key sociodemographic variables useful for the description of the study population as a whole. Nevertheless, increasing the number of these "filtering variables" in order to catch more relevant studies to explore determinants of exposure would have led to less studies selected and a lack of statistical power for analyses. As emphasized by Gonzalez-Alzaga et al. (2022), in order to facilitate the comparison of results from multi-center studies (including cross-countries studies), it would be prudent to rely on well-defined strategies and standardized procedures for the development of questionnaires to be used in future HBM studies.

3.5. Strengths and limitations

This study is the first to describe BPA exposure levels in European women in a large sample from several European countries, since the 2011–2012 European cross-sectional study conducted by Covaci et al. (2015) in the general population. The present BPA Study is based on well-designed human biomonitoring studies in Europe. The study combines data from 15 cohorts and cross-sectional studies, and had undergone rigorous post-harmonization through an innovative interagency collaborative process within HBM4EU. This study has two major limitations with respect to the original objectives of the study protocol. First, it was not possible to calculate an overall European average BPA concentration over the study period based on the data collected, *e.g.* by *meta*-analysis. This would have required the calculation of aggregated estimates taking into account the original study designs (*e.g.*, sampling design, sampling weight…), since the available data represent only

fragmented subsets of the original study populations (study coverage is variable, regional in some studies, national in others…), parameters that we did not have from the collected datasets. Second, the identification of the BPA exposure factors was not achieved because several factors were not simultaneously available for all the original studies. Nevertheless, we were able to describe the BPA exposure levels according to some key biological parameters and sociodemographic characteristics at a European-wide level. A broader range of data planned for collection in the original questionnaires of the contributing studies would have resulted in a better investigation of the determinants of BPA exposure in European women. A further limitation of this study is that, until 2018, very few HBM data on BPA exposure were available in some European countries (Thoene et al., 2018). Consequently, it was not possible to provide a more comprehensive description of BPA exposure levels in European women by including Eastern European countries. In addition, HBM BPA data from six previously identified eligible studies could not be included in this BPA Study for various reasons (*e.g.*, the original study protocols did not authorize data sharing).

- How can researchers avoid the main difficulties encountered in this study in the future?

Based on our experience in this study, we recommend that future epidemiological studies that follow an approach similar to that of the present study, aimed at combining data in order to strengthen and/or extend statistical analyses, should be able to rely on pre-harmonized study protocols including different common factors of interest, prior to the inclusion of the participating studies/countries. Such a strategy would require the inclusion of essential information for the combined analysis of data or even for the conduct of *meta*-regressions, while limiting as much as possible some of the biases inherent in any pre- and post-harmonization process. An alternative solution, which would be the most optimal but also the most restrictive in terms of cost and logistics, would be to conduct a multi-center survey according to a single pre-designed protocol, applied simultaneously in all the participating countries. This approach would allow for the construction of exposure indicators (including the determinants of exposure) that are directly representative of the broad population as a whole.

4. Conclusions

The present study has shown that there are considerable contrasts in BPA exposure levels among women in Europe from 2007 to 2014, both between and within the included studies, regardless of the sub-population group, based on the use of data from existing HBM studies. The lowest mean level of total urine BPA concentrations was observed in pregnant women in France, while the highest mean level was observed in a mother–child pair population in Belgium, and in pregnant women in Greece. In addition, there are large differences in the background levels (*e.g.,* the 95th percentiles of distribution) of BPA exposure among European women; in particular, the background level of BPA in pregnant women in Greece was 4-fold higher than the background level of BPA observed in women from the general population in Belgium-Flanders. This may be due to real geographic differences in BPA exposure, or to the possible impact of various analytical methods initially used in the contributing studies, or to the impact of a BPA variability exposure over time. Compared to the current health-based human biomonitoring guidance values for total urinary BPA in adults from the general population, European women had high levels of BPA exposure over the period 2007–2014. Given that all European women are potentially at risk from the BPA's adverse effects, strengthened population-based measures to further reduce BPA exposure are urgently needed. Finally, we found no clear determinants of total urinary BPA concentrations among European women, reflecting the variability in exposure sources across regions and populations. This work also highlights the importance of harmonizing biomonitoring study protocols in advance in order to maximize the possibilities of producing comparable and interpretable results at a European-wide scale. The process of harmonizing HBM methods and practices within European countries has been an ongoing process for several years, from the ESBIO project in 2005 to DEMOCOPHES in 2011/2012 and HBM4EU in 2017/2022. The latter has also developed an aligned study protocol (Gilles et al., 2022; Govarts et al., 2023), in which the contributing studies were pre- or post-harmonized in order to reach a better comparability, for example for bisphenols. The new EU-wide Partnership for the Assessment of Risks from Chemicals (PARC) launched in 2022 (Marx-Stoelting et al., 2023) (https://www.eu-parc.eu/). Building on the experience gained so far, it will enable further advancements in a standardized practice of human biomonitoring in Europe.

CRediT authorship contribution statement

Romuald Tagne-Fotso: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Margaux Riou:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Abdessattar Saoudi:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Conceptualization. **Abdelkrim Zeghnoun:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Conceptualization. **Hanne Frederiksen:** Writing – review & editing, Resources, Conceptualization. **Tamar Berman:** Writing – review & editing, Resources, Conceptualization. **Parisa Montazeri:** Writing – review & editing, Resources, Data curation. **Anna-Maria Andersson:** Writing – review & editing, Resources, Conceptualization. **Laura Rodriguez-Martin:** Writing – review & editing, Software, Data curation. **Agneta Akesson:** Writing – review & editing, Resources. **Marika Berglund:** Writing – review & editing, Resources. **Pierre Biot:** Writing – review & editing, Resources. **Argelia Castaño:** Writing – review & editing, Resources. **Marie-Aline Charles:** Writing – review & editing, Resources. **Emmanuelle Cocco:** Writing – review & editing. **Elly Den Hond:** Writing – review & editing, Resources. **Marie-Christine Dewolf:** Writing – review & editing, Resources. **Marta Esteban-Lopez:** Writing – review & editing, Resources. **Liese Gilles:** Writing – review & editing, Resources, Data curation. **Eva Govarts:** Writing – review & editing, Resources, Data curation. **Cedric Guignard:** Writing – review & editing. **Arno C. Gutleb:** Writing – review & editing, Resources. **Christina Hartmann:** Writing – review & editing, Resources. **Tina Kold Jensen:** Writing – review & editing. **Gudrun Koppen:** Writing – review & editing. **Tina Kosjek:** Writing – review & editing. **Nathalie Lambrechts:** Writing – review & editing, Resources. **Rosemary McEachan:** Writing – review & editing, Resources. **Amrit K. Sakhi:** Writing – review & editing. **Janja Snoj Tratnik:** Writing – review & editing, Resources. **Maria Uhl:** Writing – review & editing, Resources. **Jose Urquiza:** Writing – review & editing, Data curation. **Marina Vafeiadi:** Writing – review & editing, Resources. **An Van Nieuwenhuyse:** Writing – review & editing, Resources. **Martine Vrijheid:** Writing – review & editing, Resources. **Till Weber:** Writing – review & editing. **Cécile Zaros:** Writing – review & editing, Resources. **Elena Tarroja-Aulina:** Writing – review & editing. **Lisbeth E. Knudsen:** Writing – review & editing, Resources. **Adrian Covaci:** Writing – review & editing, Resources. **Robert Barouki:** Writing – review & editing. **Marike Kolossa-Gehring:** Writing – review & editing, Resources. **Greet Schoeters:** Writing – review & editing, Resources. **Sebastien Denys:** Writing – review & editing, Resources. **Clemence Fillol:** Writing – review & editing, Resources. **Loïc Rambaud:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary material

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