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Environment International 154 (2021) 106563

Contents lists available at ScienceDirect

Environment International

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

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Human biomonitoring (HBM)
HBM4EU
Internal exposure
Biomarkers
Endocrine disruptor
Bisphenol A (BPA)
Human biomonitoring guidance value (HBM-GV)
Physiologically-based pharmacokinetic modelling (PBPK)

ABSTRACT

The "European Human Biomonitoring Initiative" (HBM4EU) derives human biomonitoring guidance values (HBM-GVs) for the general population (HBM-GV_{GenPop}) and/or for occupationally exposed adults (HBM-GV_{Worker}) for several priority substances and substance groups as identified by policy makers, scientists and stakeholders at EU and national level, including bisphenol A (BPA).

Human exposure to BPA is widespread and of particular concern because of its known endocrine-disrupting properties. Unlike the conjugated forms of BPA circulating in the body, free BPA is known to interact with the nuclear estrogen receptors. Because free BPA is considered to be more toxicologically active than the conjugated forms (e.g. BPA-glucuronide (BPA-G) and BPA-sulfate (BPA-S)), its measurement in blood provides the superior surrogate of the biologically effective dose. However, considering the difficulty of implementing blood sampling in large HBM cohorts, as well as the current analytical capacities complying with the quality assurance (QA)/quality control (QC) schemes, total BPA in urine (i.e. the sum of free and conjugated forms of BPA measured after an hydrolysis of phase II metabolites) was retained as the relevant exposure biomarker for BPA.

HBM-GV_{GenPop} for total BPA in urine of 230 μg/L and 135 μg/L for adults and children, respectively, were developed on the basis of toxicological data. To derive these values, the concentrations of urinary total BPA consistent with a steady-state exposure to the temporary Tolerable Daily Intake (t-TDI) of 4 μg/kg bw/day set in 2015 by the European Food Safety Authority (EFSA) were estimated. The BPA human physiologically-based pharmacokinetic (PBPK) model developed by Karrer et al. (2018) was used, assuming an oral exposure to BPA at the t-TDI level averaged over 24 h. Dermal uptake of BPA is suspected to contribute substantially to the total BPA body burden, which in comparison with the oral route, is generating a higher ratio of free BPA to total BPA in blood. Therefore, an alternative approach for calculating the HBM-GV_{GenPop} according to the estimated relative contributions of both the oral and dermal routes to the global BPA exposure is also discussed.

Regarding BPA exposure at the workplace, the steady-state concentration of urinary total BPA was estimated after a dermal uptake of BPA that would generate the same concentration of free BPA in plasma (considered as the bioactive form) as would a 24 h-averaged intake to the European Chemicals Agency (ECHA)'s oral DNEL of 8 μg BPA/kg bw/day set for workers. The predicted concentration of urinary total BPA at steady-state is equivalent to, or exceeds the 95th percentile of total BPA in urine measured in different European HBM studies conducted in the general population. Thus, no HBM-GV_{Worker} was proposed, as the high background level of BPA coming from environmental exposure - mostly through food intake - is making the discrimination with the occupational exposure to BPA difficult.

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https://doi.org/10.1016/j.envint.2021.106563
Received 3 September 2020; Received in revised form 5 April 2021; Accepted 7 April 2021
Available online 23 April 2021

1. Introduction

The HBM4EU project is co-funded within the Horizon2020 research and innovation programme and operates at the science-policy interface. Within the project, HBM-GVs are derived for substances among the HBM4EU priority substances, these having been identified by EU services and national agencies in charge of chemical regulation and management in the partner countries (Ougier, et al., in preparation).

An HBM-GV is corresponding to a biomarker concentration in the biological matrix and represents a guidance value below which adverse human health effects generated by the substance exposure are not to be expected, according to current knowledge. HBM-GVs are derived within the HBM4EU project according to a systematic and transparent methodology (Apel et al. 2020) and by taking into account the feedback provided by competent experts from the 30 HBM4EU participating countries being thereby mutually agreed within the HBM4EU consortium.

The derived HBM-GVs allow for performing health risk assessments within the project, and thereby are demonstrating the feasibility and relevance of health risk assessments based on HBM data.

In the current paper, HBM-GVs for BPA in adults and children from the general population (HBM-GV_{GenPop}) and in occupationally exposed adults (HBM-GV_{Worker}) are addressed. BPA is a synthetic chemical that has been used extensively since 1940, mostly to manufacture hard, durable plastic including polycarbonate and epoxy resins. It also serves as a stabiliser in polyvinyl chloride (PVC) production. Any residual BPA present in the final products or articles made of these materials migrates into food with which it comes into contact (Geens et al. 2011). In addition, BPA release from polycarbonate may occur because of hydrolysis and decomposition over time at the polymer surface, a phenomenon that is positively correlated with an increase in temperature, time of contact and/or also pH (Pedersen et al. 2015). Ingestion of contaminated food is expected to be the leading source of human exposure to BPA, which is widespread (Rubin 2011; Vandenberg et al. 2010). BPA is also used in a wide variety of non-food related applications (e.g. paints, electronic equipment, building materials, toys, CDs, medical devices, thermal papers), which lead to an additional exposure *via* inhalative, dermal uptake and parenteral route (Anses 2011; Geens et al. 2012; Liao and Kannan 2011; Testai et al. 2016; Vandenberg et al. 2007; vom Saal and Welshons 2014).

Despite its massive use and production, very few studies have assessed occupational exposure to BPA in Europe (Ribeiro et al. 2017). Nonetheless, evidence of BPA exposure through dermal contact has been found for workers in thermal paper factories - especially those working in the manufacture of coating material and operating coating machines - as well as for workers exposed to BPA-containing thermal paper such as cashiers (Braun et al. 2011; Heinala et al. 2017; Ndaw et al. 2016). The geometric mean creatinine-adjusted total BPA level in urine (collected from 7 urine samples provided over 2 consecutive workdays) in individuals working in U.S. companies producing BPA or BPA-based products, was found to be about 70 times higher than for non-occupationally exposed adults from the U.S. general population (Hines et al. 2017b). Increased BPA air concentrations at the workplace are especially expected for activities producing BPA-containing aerosols, such as handling sacks or bags of BPA, or spilling BPA (EU RAR, 2010; Hines, 2017a).

When deriving HBM-GVs for BPA, special attention was paid to the different routes of exposure as these may influence the bioavailability of BPA as well as the concentration of free (unbound and unconjugated) BPA in the systemic circulation, which is known to elicit deleterious biological and endocrine disruptive effects (Beausoleil et al. 2018; Ginsberg and Rice 2009; Healy et al. 2015; La Merrill et al. 2020; Matthews et al. 2001; Vandenberg et al. 2013).

2. Methodology for deriving HBM-GVs for BPA

The first step of the methodology consisted in assessing the toxicokinetic and toxicodynamic properties of BPA, in order to select the most specific and sensitive exposure biomarker(s) as well as the biological matrix for sampling the biomarker(s) for use in HBM studies, which results may be used for conducting further health risk assessments in different population groups. A particular attention was also paid to the analytical capacities at EU level during this step.

The second step aimed to review the available toxicological data on BPA in order to select one of the 3 options by which HBM-GVs are derived, according to the methodology agreed on (Apel et al. 2020): as a first option, a point of departure (POD) determined from a relationship between HBM concentrations of the substance biomarker(s) and a selected critical health effect observed in humans should be considered as starting point for the derivation. If this is not possible, the second option consists in estimating the concentration of the substance's biomarker(s) that corresponds to an external toxicity reference value (TRV) set by a recognised body (preferably European) using a rigorous and transparent scientific methodology. This approach is similar to the Biomonitoring Equivalent (BE) approach developed in the U.S. by Hays et al. (Hays and Aylward 2009; Hays and Aylward 2012; Hays et al. 2007). Finally, if no TRV is available, the third option consists in extrapolating and adjusting a POD identified from a toxicological animal study.

2.1. Identification and assessment of potential biomarkers of BPA exposure

BPA entering the body *via* the oral route is transported to the liver after absorption into the mesenteric vessels. It is rapidly metabolised in the gut wall and the liver, before reaching the systemic circulation (Bernier and Vandenberg 2017; Vandenberg et al. 2014). This metabolism step mainly produces BPA-G (as monoglucuronide (BPA-MG) and diglucuronide (BPA-DG)), through uridine diphosphate-glucuronosyltransferase isoforms. BPA may also be converted by sulfotransferases to BPA-S forms (as monosulfate (BPA-MS) and disulfate (BPA-DS)) (EFSA 2008; Ginsberg and Rice 2009; Zalko et al. 2011). Therefore, the majority of BPA that circulates in the bloodstream following oral exposure corresponds to BPA conjugated forms, although some free BPA does reach the circulation. At low concentrations in humans, only about 5% BPA circulates as free (unbound to plasma proteins) fraction in the bloodstream (Csanady et al. 2002; Teeguarden et al. 2005). The BPA-conjugates are transported to the kidney *via* the blood, and further excreted in the urine. The BPA biological half-life in humans after oral exposure is estimated to be less than 6 h (Teeguarden et al. 2015; Völkel et al. 2005; Völkel et al. 2002).

In contrast to oral exposure, BPA absorbed by dermal contact or by inhalation directly enters the systemic circulation without undergoing first pass metabolism. Blood ratios of free BPA over total BPA are consequently higher when absorbed *via* skin or inhalation in comparison with the oral route. Further, a prolonged exposure resulting from the slow absorption of BPA through the skin is observed if compared to the absorption *via* the oral and probably also inhalation route (Bernier and Vandenberg 2017; Liu and Martin 2017; Mielke et al. 2011; Sasso et al. 2020; Zalko et al. 2011).

Among the identified BPA potential biomarkers of exposure, the most adapted one to reflect the human exposure to BPA was selected along with the preferred sampling type and time.

2.2. Selection of the approach for deriving HBM-GVs for BPA

Numerous epidemiological studies on BPA suggest associations between exposure and a range of health effects and diseases, including metabolic syndrome, infertility and asthma (Ranciere et al. 2015; Rezg et al. 2014; Rochester 2013). According to the 2015 EFSA opinion on

BPA for which epidemiological studies available at that time were assessed, only limited conclusions could be drawn from the available human studies on the likelihood of an association between BPA exposure (including during pregnancy) and any adverse effects (including reproductive and developmental effects), even if associations for some effects (e.g. neurodevelopmental and immune effects) were identified from prospective studies. However, these associations were not consistent across the studies and it could not be ruled out that the results were confounded by diet or concurrent exposure factors. Thus, it was concluded that the reported associations were not providing sufficient evidence to infer a causal link between BPA exposure during pregnancy or childhood and effects in humans (EFSA, 2015). Further health risk assessments conducted for BPA, as for example by the French Agency for Food, Environmental and Occupational Health & Safety (Anses) or by ECHA, met the same conclusion after having assessed available epidemiological studies (Anses 2013; ECHA 2015). Consequently, existing risk assessments on BPA have made use of epidemiological data only as supporting evidence for the selection of the critical effect, which was determined from animal toxicological data (Anses 2013; EFSA 2015).

Nonetheless, a review of epidemiological studies published since these reports has been performed, in order to assess whether human data could be used to derive an HBM-GV for BPA. Ten original studies and four *meta*-analysis were identified. Among the original studies, two have a cross-sectional design and are thus unsuitable to study BPA exposure-effect associations on their own (Ji et al. 2018; Wang et al. 2015). Four case-control studies have investigated the link between BPA exposure and diabetes and among these, three have shown an association between levels of BPA in serum or urine and some clinical parameters of glucose metabolism such as insulin resistance and adiponectin production (Dallio et al. 2018; Menale et al. 2017; Soundararajan et al. 2019). However, the number of subjects included in these studies was limited and did not reflect the general population diversity. In the Shu et al. (2018) study, no statistically significant difference in serum BPA concentrations was observed between patients with type 2 diabetes and the controls. Another study, Hu et al. (2019), has reported an increased risk of myocardial infarction in patients with type 2 diabetes associated with BPA detection in spot urine samples. Finally, the prospective study from Bi et al. (2016) did not found any evidence suggesting that relatively higher levels of BPA *per se* would hasten the development of diabetes in middle-age or older adults in China. In summary, there is only limited evidence about a causal link between BPA and metabolic disease considering the human data published up to now.

Thus, the derivation of HBM-GVs for BPA could not be based on any solid relationship between BPA exposure biomarker concentrations and an adverse health effect observed in humans.

The applicability of the second option for deriving HBM-GVs was thus explored, thereby involving the following steps: i) Identification and review of existing TRVs set by recognized bodies; ii) Assessment of the available TRVs in order to select the most relevant one to be used as starting point for the HBM-GV derivation, and iii) Selection of a toxicokinetic extrapolation approach in order to estimate the selected internal exposure biomarker(s) concentration consistent with the selected TRV.

Toxicokinetic extrapolation of a TRV into equivalent concentration (s) of the selected biomarker(s) of exposure can be performed either with a simple mass balance equation in the case of urinary biomarker(s) (which is equivalent to a single-compartment PK model), a multi-compartments PK model or also a PBPK model (Hays and Aylward 2009; Hays et al. 2007). As part of a task dedicated to PK and PBPK modeling within the HBM4EU project, available human PBPK models for BPA were identified and reviewed (Edginton and Ritter 2009; Karrer et al. 2018; Sarigiannis et al. 2016; Sharma et al. 2018; Shin et al. 2004; Teeguarden et al. 2005; Yang et al. 2015). Building on this work and considering the routes of exposure included in the models and the availability of the PBPK modelling code, a model was selected to calculate the HBM-GVs for BPA. As the second option for deriving a HBM-GV turned out feasible, the third option (adjusting a POD) was not needed.

3. Results

3.1. Selection of a BPA biomarker of exposure

The potential biomarkers of exposure identified for BPA are summarised in Table 1, along with the advantages and disadvantages for their use in biomonitoring studies.

From a toxicological point of view, the concentration of free BPA in blood turns out to be the most relevant metric dose as it is well known to interact with the estrogen receptor (unlike the BPA-G forms) (Matthews et al. 2001), thereby representing the bioactive form of BPA. However, as BPA undergoes an extensive first-pass hepatic metabolism *via* glucuronidation and sulfatation after oral exposure (the most prominent route of environmental exposure), blood and urine concentrations of free BPA following exposure to environmentally relevant doses of BPA are very low. However, even if analytical methods to measure very low levels of free BPA in serum or plasma have recently become available and progress has been achieved regarding the QA/QC provisions to prevent external contamination to BPA, few laboratories at this time have the capacity to perform these measurements with appropriate sensitivity and according to QA/QC criteria.

BPA-G, which is the major form of BPA present in blood (plasma) and urine, is a specific BPA exposure biomarker that is not prone to external contamination as it requires *in vivo* metabolism to be produced (Völkel et al. 2005; Völkel et al. 2002; Völkel et al. 2008). Thus, BPA-G is considered a good candidate biomarker of exposure even though it is expected to be much less informative in terms of biological effects than concentrations of free BPA in the plasma or the serum. Nevertheless, β-glucuronidase present at high concentrations in the liver, kidney, intestine, and placenta has the capacity to deconjugate BPA-G into free BPA, possibly thereby reactivating BPA's capacity to affect endocrine signalling pathways (Ginsberg and Rice 2009).

BPA-S is also a specific biomarker of exposure that can be measured in blood (plasma) and urine, but its concentration level and consequently its rate of detection is much lower than for BPA-G (Andra et al. 2016). Both BPA-G and BPA-S are prone to inter-individual, inter-life stage and excretion compartment variability (e.g. breast milk *versus* urine). Another limitation for their use as exposure biomarkers is that conjugated forms may degrade to some extend if the urine samples are stored at room temperature (Waechter et al. 2007; Ye et al. 2007), which may lead to underestimation of BPA exposure if the conjugated forms alone are measured directly in the biological sample. Unfortunately, quantifying the eventual degradation of the BPA forms occurring in urine samples during the period from their collection to their analysis in the laboratory remains a real challenge (Andra et al. 2016).

Nowadays, analytical methods permitting the simultaneous detection of free BPA and its conjugate exist (Andra et al. 2016; Battal et al. 2014; Lacroix et al. 2011). These methods allow for determining total BPA by adding the individually measured levels of free and conjugated BPA. Nevertheless, not all the conjugated forms of BPA present in a sample can be accurately quantified by this approach, because of the lack of analytical standards for certain BPA conjugates. Thus, it can be considered that a form of uncertainty in the estimation of the BPA levels present in a biological sample is induced with these direct methods.

Quantification of total BPA (free plus conjugated forms of BPA) level can be achieved by measurement of free BPA after an appropriate enzymatic preparation treatment of the samples in order to deconjugate the BPA glucuronide and sulfate forms. During the sample preparation, special caution should be paid to the potential external contamination with free BPA (possibly occurring because of BPA-containing sample collection equipment for example), that may result to inflated total BPA concentrations. It can be noticed however that this critical issue appears nowadays under control at least in a number of laboratories as attested

Table 1
Advantages and disadvantages of the potential BPA biomarkers of exposure (adapted from Krishnan et al. (2010)).

Analyte	Biological matrix	Advantages	Disadvantages
Free BPA	Blood	Specific biomarker of exposure; expected to be relevant to potential adverse effects as circulating biologically active form	Short half-life (especially limiting for spot samples) (Thayer et al., 2015); very low concentration levels (in general population) not yet compatible with most of existing analytical methods and inducing a difficulty to be distinguished from possible background external contamination; invasive sampling required
	Urine	Specific biomarker of exposure; non-invasive sampling	Little BPA excreted unchanged in urine (Völkel et al. 2008); low concentration levels (in the general population) inducing a potential difficulty to be distinguished from possible external background contamination; not a good indicator of BPA in blood (poor correlation ($r = 0.51$) between molar concentration of BPA in plasma and that in urine due to rapid metabolism (Ho et al. 2017))
BPA-G	Blood	Specific biomarker of exposure	Short half-life in humans (especially limiting for spot samples) (Khmiri et al. 2020; Teeguarden et al. 2015); not directly relevant to mode of action; invasive sampling required
	Urine	Specific biomarker of exposure; major urinary metabolite for BPA (Völkel et al. 2005; Völkel et al. 2002); non-invasive sampling	Not directly relevant to mode of action
BPA-S	Blood	Specific biomarker of exposure	Less present than BPA-G; Short half-life in humans (especially limiting for spot samples) (Khmiri et al. 2020) not directly relevant to mode of action; invasive sampling required
	Urine	Specific biomarker of exposure; non-invasive sampling	Less present than BPA-G (Khmiri et al. 2020); not directly relevant to mode of action
Total BPA	Blood	Specific biomarker of exposure; integrated measure of the circulating BPA free form and conjugated forms	Not directly relevant to mode of action; appropriate QA/QC provisions necessary to control the possible background external contamination of the samples; invasive sampling required;
	Urine	Specific biomarker of exposure; preferred matrix for short half-live substances; non-invasive sampling	Not directly relevant to mode of action; appropriate QA/QC provisions necessary to control the possible background contamination of the samples

BPA-G: bisphenol A glucuronide; **BPA-S**: bisphenol A sulphate.

by the results of the different ICI/EQUAS performed in the frame of the HBM4EU project where this aspect was a matter of attention (HBM4EU 2019a; HBM4EU 2019b; HBM4EU 2019c; HBM4EU 2020). This indirect measurement of total urinary BPA was considered to be the best option to assess exposure to BPA within the HBM4EU project (Thomsen et al. 2017) despite the recent results by Gerona et al. (2020) reporting that indirect techniques requiring deconjugation are underestimating actual human levels of BPA. Indeed, as indicated by Calafat et al. (2020), numerous data do not support the view that the indirect methods underestimate urinary BPA concentrations and thus BPA exposure. Consequently, the 4 rounds of inter-laboratory comparison investigations and external QA schemes conducted for the analysis of BPA within the framework of the project were focused on urinary total BPA as exposure biomarker (HBM4EU 2019a; HBM4EU 2019b; HBM4EU 2019c; HBM4EU 2020).

Regarding the occupational field, a spot-urine collection is recommended at the end of the work shift, as usually recommended for exposure biomarkers with short half-lives. This sampling time is indicated for assessing BPA exposure that has occurred during the prior working shift.

3.2. Derivation of an HBM-GV for BPA in the general population

3.2.1. Review of existing BPA toxicity reference values for the general population

Oral TRVs for BPA set by the US EPA (1993), Health Canada (2008), EFSA (2015) and ECHA (2015) were identified (ECHA 2015; EFSA 2015; Health Canada 2008; US EPA 1993). Both, the provisional TDI (p-TDI) of 25 μg/kg bw/day and the reference dose (RfD) of 50 μg/kg bw/day by respectively Health Canada and the US EPA are based on the reduction in body weight observed in different rodent studies after chronic BPA exposure (a 3-generation rat study by Tyl et al. (2002) supported by the 2-generation mouse study by Tyl et al. (2008) for Health Canada; a 2-year study in both rats and mice by the NTP (1982) for the US EPA) (Krishnan et al. 2010).

In 2012, EFSA's expert Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids undertook a full re-evaluation of the human risks from exposure to BPA through the diet, also taking into consideration the contribution of non-dietary sources of exposure to BPA. By considering the available human and animal evidence prior to 2015, the estimated "likely" effects of BPA (i.e. increase of liver and kidney weight and mammary gland proliferation) were brought forward for dose–response analysis and for defining the reference point for a t-TDI value (ECHA 2015). The mean F0 relative kidney weight increase in the 2-generation study in mice by (yl et al. (2008) was thereby used as critical endpoint, for which a Benchmark Dose 10% Lower Confidence Limit ($BMDL_{10}$) of 8.96 mg/kg bw/day was calculated. This dose in mice was extrapolated to an oral Human Equivalent Dose (HED) by application of a Human Equivalent Dose Factor (HEDF) of 0.068, equivalent to the ratio of BPA-specific area under the curve (AUC) values for free BPA in serum across mice and humans. While AUC values of free BPA in serum after oral dosing of adult and new-born CD-1 mice were available from toxicokinetic experiments, AUC values for human adults after oral exposure were predicted using the human PBPK model by Yang et al. (2013). Multiplying the mice $BMDL_{10}$ by the HEDF, a HED value of 609 μg/kg bw/day was obtained. Finally, application of an overall assessment factor (AF) of 150 (AF of 10 to account for intra-species differences; AF of 2.5 for inter-species toxicodynamic differences; and AF of 6 for remaining uncertainties about possible toxic effects below the dose at which effects on the kidney are observed, i.e. regarding mammary gland, reproductive, neurobehavioral, immune and metabolic systems) to this HED led to a t-TDI value of 4 μg BPA/kg bw/day (Table 2). This TDI was made temporary, as EFSA committed to re-evaluate BPA toxicity again, taking into account more recent data and in particular a two-year study by the U.S. National Toxicology Program (CLARITY-BPA program) (EFSA 2017).

Table 2
EFSA's and ECHA's toxicity reference values for BPA in the general population.

Agency	Key study	Endpoint	Point of departure (µg/kg bw/day)	Assessment factors	Toxicity reference value
EFSA (2015)	Tyl et al. (2008) (mouse two-generation toxicity study)	Increased relative mean kidney weight in male F0 adult mice	$BMDL_{10}$ = 8960 HED = 609 with HEDF = 0.068	**150** − 2.5 for interspecies differences − 10 for intra-species differences − 6 for the uncertainty in the database	**t-TDI** **4 µg/kg bw/day**
ECHA (2015)	Tyl et al. (2008) (mouse two-generation toxicity study)	Increased relative mean kidney weight in male F0 adult mice	$BMDL_{10}$ = 8960 HED = 609 with HEDF = 0.068 $BMDL_{10}$ = 8960 HED = 6.24 or 6.64 with conversion factor 'oral mouse' to 'dermal human' either 1436.9 or 1350.4 depending upon PBPK model used (Mielke et al. 2011; Yang et al. 2013)	**150** − 2.5 for interspecies differences − 10 for intra-species differences − 6 for the uncertainty in the database	**oral DNEL** **4 µg/kg bw/day** **DNEL for dermally absorbed total BPA dose** **0.1 µg/kg bw/day** (with assumed skin biotransformation rate of 50%)

BMDL = lower confidence limit of the benchmark dose level; **DNEL** = derived no effect level; **HED** = human equivalent dose; **HEDF** = human equivalent dose factor; **t-TDI** = temporary tolerable daily intake.

EFSA's t-TDI derivation approach was supported by ECHA's Risk Assessment Committee (RAC), which endorsed the value of 4 µg BPA/kg bw/day as DNEL for oral exposure in the general population (ECHA 2015). Based on the same HED approach, the RAC also derived a DNEL value of 0.1 µg/kg bw/day for a dermally absorbed total BPA dose in the general public. To this end however, predictions of serum concentration–time profiles and estimations of internal dose metrics for free BPA following oral and dermal exposure were modelled by a different human PBPK model (Mielke et al. 2011) that includes both the oral and dermal exposure routes. These predictions enabled the RAC to calculate a conversion factor 'oral mouse' to 'dermal human', allowing for converting the $BMDL_{10}$ for alteration of the mice kidney weight into a dermal HED. Application of the same AFs as for the oral DNEL (equivalent to the t-TDI) and assumption of a BPA biotransformation rate in the skin of 50% (assuming thereby that only half of a BPA dose absorbed by the skin may reach the systemic circulation as free BPA), resulted in a DNEL for a dermally absorbed dose of 0.1 µg BPA/kg bw/day (rounded value). In the worker's BPA exposure assessment *via* BPA-containing thermal paper, RAC considered a 10% skin absorption rate, as used by default in the EU risk assessment report and by EFSA (EFSA 2015; EU RAR, 2010).

Lower health-related benchmark values have been used by national risk assessment bodies in the context of health risk assessments on BPA, but these values do not constitute as such recommended TRVs considering the uncertainties underlying the selected studies and POD (Anses 2013; Beausoleil et al. 2018; Danish EPA 2012; KEMI 2013).

3.2.2. *Selection of a toxicity reference value to derive the HBM-GV_{GenPop}*

The assessment of the available TRVs led to retain the EFSA t-TDI value of 4 µg/kg bw/day (identical to ECHA's oral DNEL for BPA exposure in the general public) as limit value to be translated into the corresponding BPA exposure biomarker concentration. This value is indeed the most recent among the TRVs identified and is resulting from a transparent scientific assessment by an EU expert panel having implemented a weight of evidence approach.

3.2.3. *Toxicokinetic extrapolation*

The eight-compartments PBPK model for BPA implemented in R published by Karrer et al. (2018) was used to predict the concentrations at steady-state of free and total BPA (free BPA + BPA-G + BPA-S) in plasma and in urine after an exposure to the t-TDI set by EFSA (equivalent to ECHA's oral DNEL for the general population). This model is based on the one developed by Yang et al. (2015) for BPA oral exposure (this latter having been used by EFSA for the HEDF calculation (ratio of AUC_{Animal}/AUC_{Human}) and further setting of the t-TDI), but was readjusted considering HBM data (free and total BPA concentrations in serum and total BPA in urine measured after BPA oral exposure in volunteers by Thayer et al. (2015) and was extended to include the dermal exposure pathway.

The HBM-GV_{GenPop} was obtained by using this PBPK model for estimating the concentration of the selected biomarker of exposure, i.e. total BPA in urine, corresponding to a steady-state exposure at the selected TRV of 4 µg/kg bw/day set by EFSA.

Two exposure scenarios were thereby tested, as follows:

- **Scenario 1** assuming a constant 24 h-averaged oral exposure to the t-TDI of 4 µg BPA/kg bw;

- **Scenario 2** assuming a constant 24-averaged exposure *via* dermal absorption that is leading to reach the same free BPA (considered as the BPA bioactive form) plasmatic concentration at steady-state, as estimated in Scenario 1.

While setting the PBPK parameters, oral BPA doses were considered completely absorbed and then conjugated with a strong first pass hepatic effect. Regarding the dermal uptake, a 60% absorption fraction with an absorption half-life of 0.167 h was considered, which are parameters supported by the findings of Biedermann et al. (2010) for exposure to BPA-containing personal care products. The uptake period considered is 24 h, a value supported by the study of Demierre et al. (2012). No skin biotransformation rate is hereby assumed. Following parameters were considered: a BPA skin tissue/serum partition coefficient of 2.15 (according to Doerge et al. (2011) and Zhang and Zhang (2006)), a tissue volume of 4.52% of 70 kg bodyweight and a fractional blood flow of 0.44. The PBPK model outputs of excreted urinary BPA quantities were converted into urinary BPA concentrations, by assuming a urinary excretion rate of 0.05 L/h and 0.023 L/h, for respectively adults and children.

Simulations and results obtained for a 70 kg male individual are detailed hereafter. The same simulations were also performed assuming a 19 kg child, which is equivalent to an age of around 5 years (figures available in suppl. data).

3.2.3.1. Scenario 1: 100% oral exposure to BPA. The steady-state concentration of free BPA in plasma for an adult of 70 kg, as predicted by the PBPK model from Karrer et al. (2018) after an oral exposure to BPA equivalent to the 24 h-averaged t-TDI dose, is equal to 0.03 nmol/L ($6.8{\cdot}10^{-3}$ µg/L) (Fig. 1). Under this scenario, the **predicted steady-state concentration of total BPA in urine is 1022 nmol/L (233 µg/**

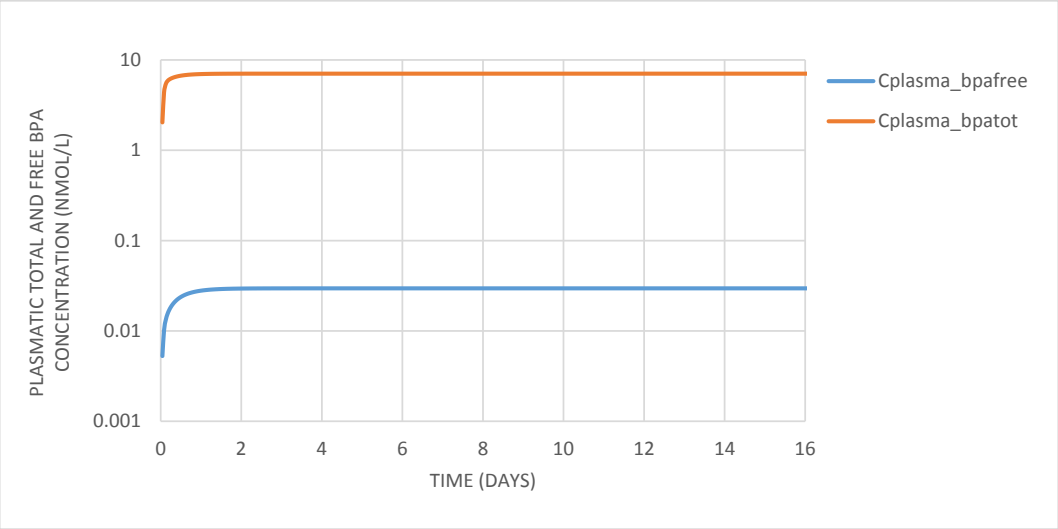

Fig. 1. Predicted steady-state free BPA (and total BPA) **plasmatic concentrations (nmol/L)** for a 70 kg adult after a 24 h-averaged continuous **oral exposure** to 4 μg BPA/kg bw *(logarithmic scale)*.

L), whereas the predicted concentration of free BPA in urine is 0.9 nmol/L (0.2 μg/L) (Fig. 2). For a 19 kg-weighting child, the predicted steady-state concentration of free BPA in plasma under this exact same scenario is 0.06 nmol/L ($13.7 \cdot 10^{-3}$ μg/L) and the **predicted concentration of total BPA in urine is 603 nmol/L (137 μg/L)** (see Supplementary Data).

3.2.3.2. Scenario 2: 100% dermal exposure to BPA. As free BPA in plasma is suspected to be responsible for the toxicity of BPA, concentration of free plasmatic BPA predicted through scenario 1, i.e. 0.03 nmol/L ($6.8 \cdot 10^{-3}$ μg/L), was considered as a threshold level above which adverse effects due to BPA could occur. The dermal dose of exposure necessary to generate an equivalent free BPA plasmatic concentration of 0.03 nmol/L was determined being 0.175 μg/kg bw/day considering the bioavailability and metabolism of BPA after skin exposure. With this BPA dermal exposure dose, the predicted steady-state concentration of total BPA in plasma is 0.3 nmol/L (Fig. 3), a much lower concentration than as predicted in Scenario 1 (~7 nmol/L, see Fig. 1). The **predicted concentration of total BPA in urine resulting is 27 nmol/L (6.2 μg/L)** (Fig. 4). For a 19 kg-weighting child, the modelled dermal dose of BPA that would generate a free BPA plasmatic steady-state concentration of 0.06 nmol/L ($13.7 \cdot 10^{-3}$ μg/L) (that corresponds to a 24 h-averaged oral uptake of 4 μg BPA/kg) is resulting in a **predicted concentration of total BPA in urine of 56 nmol/L (12.8 μg/L)**.

3.2.4. Conclusion on the HBM-GV$_{GenPop}$ values

Table 3 summarises the estimated concentrations of total BPA in urine for a 70 kg adult, after either a 100% oral or a 100% dermal exposure, that would generate the same free BPA steady-state concentration in plasma as that obtained after a 24 h-averaged oral exposure to 4 μg/kg bw. Results are also given when setting the PBPK physiological parameters to correspond to a 19 kg child.

As food intake is likely to be the major contributor to the overall BPA exposure in the general population, the concentrations of total BPA in urine estimated after the 100% oral exposure scenario were selected as HBM-GV$_{GenPop}$, giving HBM-GV$_{GenPop}$ of rounded **230 μg/L** and **135 μg/L** for respectively adults and children (older than 3 years, considering the daily urinary rate used in the simulations).

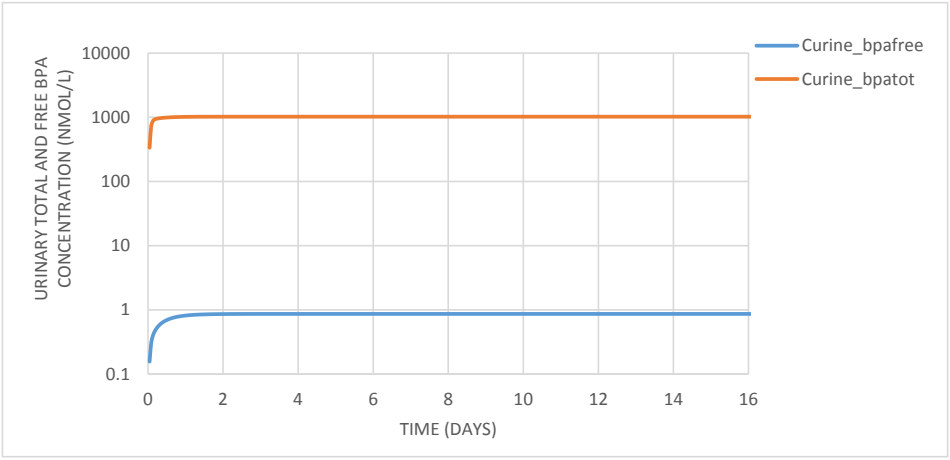

Fig. 2. Predicted steady-state total BPA (and free BPA) **urinary concentrations** (nmol/L) for a 70 kg adult after a 24 h-averaged continuous **oral exposure** to 4 μg BPA/kg bw *(logarithmic scale)*.

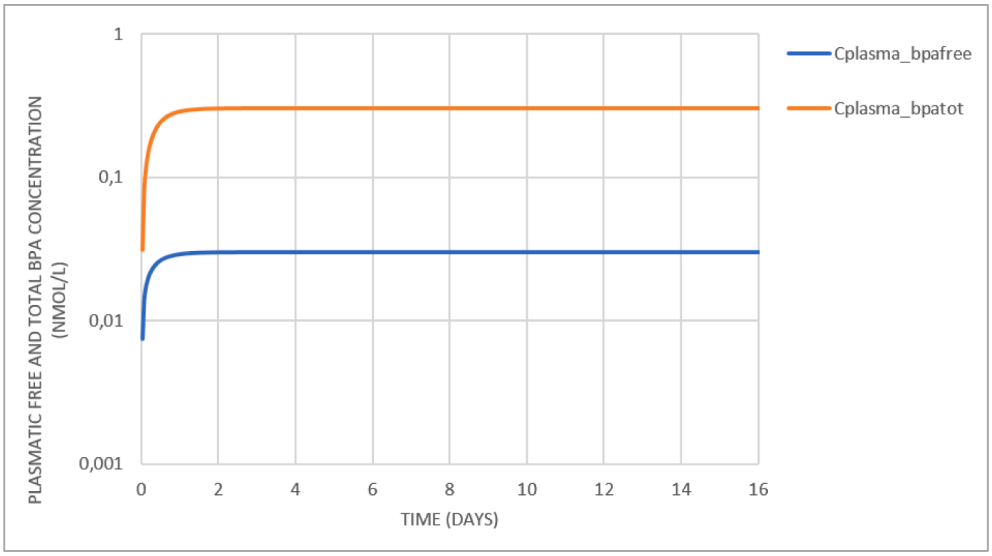

Fig. 3. Predicted steady-state free BPA (and total BPA) **plasmatic concentrations (nmol/L)** for a 70 kg adult after a 24 h-averaged continuous **dermal exposure** that generates the same concentration of free BPA in plasma than as predicted in Scenario 1 (0.03 nmol) *(logarithmic scale)*.

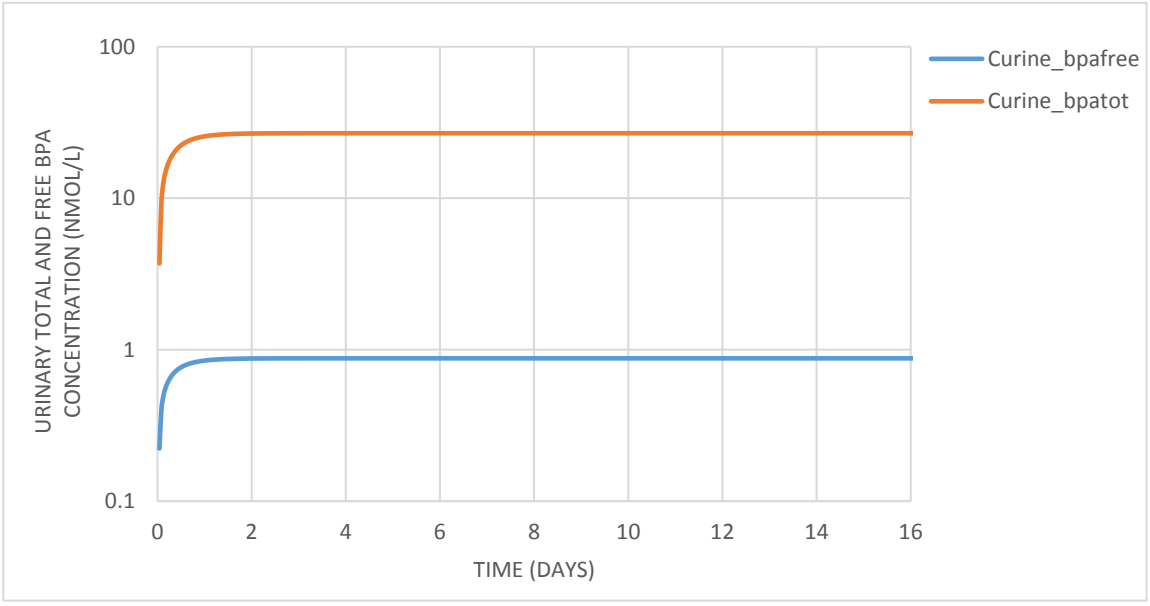

Fig. 4. Predicted steady-state free BPA (and total BPA) **urinary concentrations (nmol/L)** for a 70 kg adult after constant and continuous **dermal exposure** that generates the same concentration of free BPA in plasma than Scenario 1 *(logarithmic scale)*.

Table 3
Concentrations of total BPA in urine after either a 100% oral or a 100% dermal exposure, both consistent with the steady-state concentration of free BPA in plasma after a 24 h-averaged oral continuous exposure to the t-TDI of 4 μg BPA/kg.

Population group	Free BPA concentration in plasma at steady-state obtained after a 24 h-averaged 100% oral exposure to the t-TDI of 4 μg/kg bw	Corresponding total BPA concentration in urine	
		Assuming a 100% oral BPA exposure	Assuming a 100% dermal BPA exposure
Adult (70 kg)	$6.8 \cdot 10^{-3}$ μg/L	**233 μg/L**	6.2 μg/L
Child (19 kg)	$13.7 \cdot 10^{-3}$ μg/L	**137 μg/L**	12.8 μg/L

3.3. Derivation of an HBM-GV for BPA in occupationally exposed adults

3.3.1. Review of existing BPA toxicity reference values for occupationally exposed adults

Occupational exposure limits (OELs) for BPA, as inhalable fraction, were set by the German Research Foundation (DFG), the Scientific Committee on Occupational Exposure Limits (SCOEL) and the Health Council of the Netherlands at respectively, 5 mg/m^3, 2 mg/m^3 and 3.3 mg/m^3 (DFG 1996 (updated in 2011); Health Council of the Netherlands 2019; SCOEL 2014). All three OELs are based on respiratory tract irritation observed in the same subchronic study, in which rats were exposed daily to airborne BPA (Nitschke et al. 1988).

The RAC proposed both oral and dermal DNELs for workers, using the same data and HED approach as for the setting of the general population DNELs but using a default AF accounting for intra-species differences of 5 for workers (instead of 10 for the general population).

Worker's DNEL values are thus two-fold the ones set for the general population: 8 μg/kg bw/day as oral DNEL for workers and 0.2 μg/kg bw/day as DNEL for dermally absorbed total BPA dose in workers.

3.3.2. Selection of a toxicity reference value as starting point to derive the HBM-GV$_{Worker}$

Due to the paucity of toxicokinetic data after inhalation of BPA, and the fact that all identified OELs are based on non-systemic respiratory effects, it is not appropriate to derive an HBM-GV$_{Worker}$ based on atmospheric BPA levels likely to induce toxic effects at the workplace.

The DNEL for dermally absorbed BPA for workers set by ECHA (2015) could have been considered directly as starting point for the HBM-GV$_{Worker}$ derivation. This value was set after route-to-route extrapolation of the oral BMDL$_{10}$ of 8960 μg/kg bw/day, further assuming a skin biotransformation rate for BPA of 50%. However, the human dermal-to-oral route equivalence factor which was used by ECHA to convert an external dermal exposure into an equivalent oral exposure, was calculated with estimates given by the Mielke et al. (2011) PBPK model. This model is a different model than the one from Yang et al. (2013) used to simulate the species-to-species extrapolation (from mice to human) for oral exposure. Using the latter model would have resulted in a 7.6 fold higher dermal-to-oral route equivalence factor, considering the differences between the two models in predicted AUCs for oral exposure and dermal exposure (EFSA 2015). Therefore, it was considered more reasonable to take advantage of the availability of the PBPK model from Karrer et al. (based on the Yang et al. model but further re-calibrated), which includes both the oral and dermal routes of exposure. Through the implementation of a reverse dosimetry approach, this model allowed us to estimate the concentration of total BPA in urine after a dermal exposure to BPA that would be consistent with the plasmatic steady-state concentration of free BPA obtained after a 24 h-averaged intake to the oral DNEL for workers of 8 μg BPA/kg bw.

3.3.3. Toxicokinetic extrapolation

A 24 h-averaged oral exposure to the oral DNEL for workers of 8 μg BPA/kg bw is leading to a free BPA plasmatic steady-state concentration of 0.06 nmol/L (13.6.10^{-3} μg/L), considered as the threshold value without appreciable health risk over a working lifetime. A daily dermal dose of 0.350 μg BPA/kg bw leading to this concentration was estimated by means of a reverse dosimetry approach with the Karrer et al. PBPK model. The concentration of total BPA in urine after a 24 h-averaged exposure to this dermal dose was estimated to be **54 nmol/L (12.4 μg/L)**.

Another simulation, still based on a constant 100% dermal exposure to BPA excluding any oral contribution to the exposure, but this time considering an occupational exposure scenario (i.e. 8 working hours/day over 5 consecutive working days) was also performed (Fig. 5). In that simulation, the steady-state concentration of free BPA in plasma at 0.06 nmol/L (13.6.10^{-3} μg/L) as limit value not to be exceeded at the end of the shift and working week was set and the corresponding **urinary concentration of total BPA** was estimated at **51 nmol/L (11.6 μg/L)**.

3.3.4. Conclusion on the HBM-GV$_{Worker}$ value

A concentration of **rounded 12 μg/L total BPA in urine** was obtained with our calculations as biological threshold value not to be exceeded in workers, when assuming only dermal exposure to BPA would occur at the workplace. This value is however lower than many of the P95 of the total urinary BPA distributions measured in adults from the EU general population (ranging from about 5 to 15 μg/L, according to e.g. Balicco et al. (2019), Covaci (2015), Dereumeaux et al. (2017), Geens (2014), Hartmann et al. (2016) and SPF (2019)). Thus, biomonitoring using total BPA in urine as biomarker for assessing exposure occurring at the workplace may not allow for identifying risky occupational exposures, considering the high background levels of BPA that originates mostly from the non-occupational intake by individuals.

Therefore, no HBM-GV$_{Worker}$ was recommended within HBM4EU for conducting occupational health risk assessments, nor for the control of the health risks related to BPA in the practice of occupational health.

4. Discussion and conclusion

4.1. Selection of the toxicological reference value and toxicokinetic extrapolation into the HBM-GV$_{GenPop}$

When deriving an HBM-GV starting from an already existing TRV, preference is given to select a TRV set through a well-documented approach chosen by a European body, as e.g. TDIs derived by EFSA or DNELs set by ECHA, unless a reliable value based on more recent and/or robust data or other considerations seems more appropriate. Concerning BPA, it was decided to rely on the EFSA's t-TDI (also adopted as oral DNEL for the general population by ECHA), even if it has to be mentioned that several studies published after EFSA's and ECHA's assessments are suggesting that BPA causes developmental effects at exposure levels far below the critical dose identified by EFSA (Hessel et al. 2016; Lind et al. 2019; Pouzaud et al. 2018). Health assessment reports produced by national bodies such as Anses, the Danish

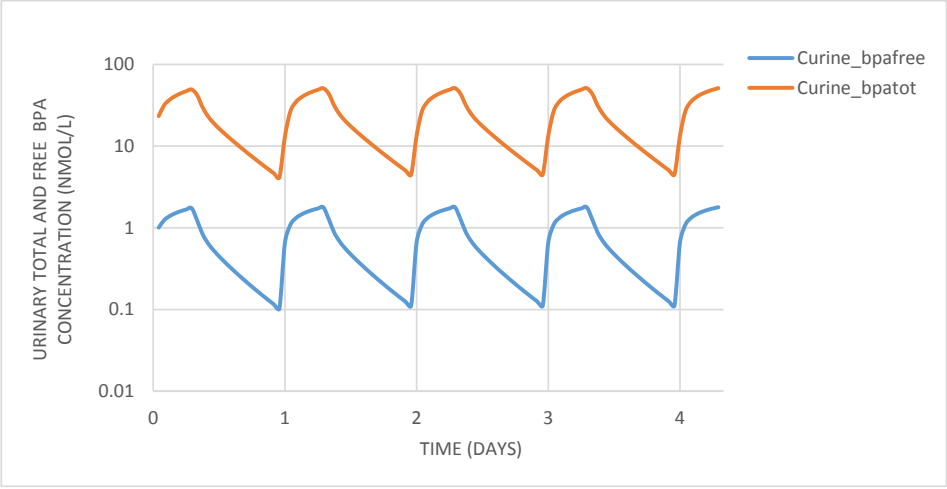

Fig. 5. Predicted urinary total (and free BPA) concentrations (nmol/L) for a 70 kg adult, after a **discontinuous dermal exposure (8 h/day over 5 consecutive days)** occurring at a constant rate and that generates the same concentration of free BPA in plasma at the end of the workshift and working week than a 24-averaged oral intake of 8 μg/kg bw at constant rate *(logarithmic scale)*.

Environmental Protection Agency (EPA) or the Swedish Chemicals Agency or the Dutch National Institute for Public Health and the Environment also consistently concluded that effects were observed at doses below those that had been considered by EFSA in setting its previous TDI value of 50 μg/kg bw/d (EFSA 2007), and now also its current t-TDI value of 4 μg/kg bw/d (Anses 2013; Danish EPA 2012; KEMI 2013; RIVM 2015). In comparison with the TDI or t-TDI, lower benchmark values based on effects observed for example in the rodents developing mammary gland were used to conduct BPA health risk assessment (Anses 2013; KEMI 2013). Nonetheless, these national bodies acknowledged in their respective health risk assessment that no single study was considered reliable enough to serve alone as a key study for the derivation of a lower TRV in comparison with EFSA's previous TDI and current t-TDI. The effects on the mammary gland were considered 'likely' by EFSA, but the choice of a solid key study and POD characterising this endpoint was also not deemed possible. More recently, data obtained in the academic parts of the "Consortium Linking Academic and Regulatory Insights on BPA Toxicity" (CLARITY-BPA) study (a comprehensive "industry-standard" Good Laboratory Practice-compliant 2-year chronic exposure study of BPA toxicity that was supplemented by hypothesis-driven independent investigator-initiated studies) are in favor of effects of BPA at low doses (Heindel et al. 2020). Effects in the prostate, or in the mammary gland or the heart have been reported at a 2.5 μg BPA/kg bw/day dose. However, the Camacho et al. (2019) paper related to the "core" study of CLARITY is reporting a possible relationship between the increased incidences of lesions in the female reproductive tract and the male pituitary gland and BPA exposure at the highest level tested (i.e. 25,000 μg/kg bw/day), whereas effects observed at lower doses do not demonstrated a consistent interpretable pattern with biological plausibility, according to the authors.

Thus, it was decided for now to adopt the EFSA's t-TDI value (equivalent to ECHA's oral DNEL for the general population) as starting point for the derivation of the HBM-GV_{GenPop} within HBM4EU, considering that a working group of scientific experts appointed by EFSA is currently reassessing the potential effects of BPA by reviewing the data on BPA published since 2013 (the cut-off point of EFSA's 2015 assessment). This reassessment will in particular consider the findings of the CLARITY-BPA project. As the selected endpoint and critical dose to set a TDI for BPA may change depending on the new available evidences, the hereby derived HBM-GVs based on the 2015 t-TDI should be updated accordingly.

The hereby derived HBM-GV_{GenPop} are almost similar to the German HBM-I values for total BPA in urine that were also calculated based on the EFSA t-TDI value of 2015 (200 μg/L and 100 μg/L for adults and children, respectively), however with a mass balance approach (Apel et al. 2017; German HBM Kommission 2012 (updated in 2015)). Biomonitoring Equivalents for BPA corresponding to the p-TDI from Health Canada (2008), RfD from the US EPA (1993) and TDI set by EFSA in 2006 (50 μg/kg bw/day) were estimated by Krishnan et al. (2010). These BEs were calculated based on a mass-balance approach and on specific BPA urinary excretion data in humans. In comparison to the BE corresponding to the 2006 TDI value by EFSA, the calculated HBM-GV_{GenPop} are updated estimates of the limit values allowing for interpreting general population HBM data for BPA. It is obtained also through an alternative approach by means of considering the concentration of free BPA in plasma as the toxicologically relevant dose metric as well as the use of a recently-released human refined and re-calibrated PBPK model against concentrations of free BPA in serum measured by Thayer et al. (2015).

4.2. Considerations associated with the biological sampling for interpreting the results using the HBM-GV_{GenPop}

Considering the environmental exposure pattern to BPA, as well as its short biological half-life (less than 6 h after oral exposure) (Teeguarden et al., 2005; Thayer et al., 2015; Völkel et al., 2002), the concentration of total BPA from a spot urine sample cannot be used to reflect a realistic estimate of an individual daily BPA exposure (Ye et al. 2011).

Therefore, 24-hour urine collections allowing for measurement of both the urinary concentration of total BPA as well as the urinary daily output rate (mL/day) would be preferable. However, collecting 24-hour urine voids in large biomonitoring studies is rarely feasible, mainly for reasons of cost and logistics.

A non-random, single-sample sampling such as the collection of first morning urine voids bears the potential of introducing a bias by not representing the daily variability and may result in an over- or under-estimation of average exposure (Christensen et al. 2012; EFSA 2015; Vernet et al. 2017).

Yet, sets of spot urine samples from a large investigated population can be used to obtain a reliable estimate of the average BPA exposure, provided that the sampling is at random in relation to meal ingestion and bladder-emptying times (EFSA 2015; Ye et al. 2011). The high numbers of samples will average out the variations in urinary concentrations of total BPA arising from temporal factors within a day (e.g. time elapsed between urine collection and the last food consumption and last urination) and across days (e.g variable daily diets), as pointed by Dekant and Völkel (2008), Vernet et al. (2017) and Ye et al. (2011)). The latter having characterized the within-day, between-day and between-week variability of phenol (e.g. BPA) urinary biomarker concentrations during pregnancy, and came to the same conclusion that for biomonitoring purposes in a large cohort (and not for etiological studies), collecting spot biospecimens was a good option. The derived HBM-GV_{GenPop} can therefore allow for interpreting BPA exposure levels measured in a large population, as planned within HBM4EU, provided spot-urine samples have been collected at random times during the day.

4.3. Alternative approach for calculating the HBM-GV_{GenPop} considering the dermal route of exposure

Estimated relative contributions of the ingestion, inhalation and dermal routes to the BPA total exposure were calculated by EFSA for different age- and gender groups (EFSA 2015). The estimations are pointing out that the inhalation route seems to contribute very little to the overall exposure to BPA for the general population, whereas the dermal route could contribute very significantly over the total intake for some age groups. As BPA entering the body *via* the dermal route circumvents first-pass metabolism, significantly more BPA in the free form circulates in the bloodstream in comparison with the oral route of exposure.

Considering this difference in toxicokinetics between the absorption routes is therefore important, explaining why we used a PBPK model including both the oral and dermal BPA exposure routes, for estimating the urinary total BPA concentrations resulting from either oral or dermal exposures. Concentrations of urinary total BPA are also proposed for mixed oral/dermal pathway scenarios (Table 4). These were calculated for exposure doses that are generating each time the same steady-state concentration of free BPA in plasma (the toxicological-relevant metric)

Table 4
Estimated urinary total BPA steady-state concentrations according to various relative contributions of the oral and dermal exposure routes to the BPA total exposure in the general population.

Relative contributions of the oral and dermal routes of exposure to the overall BPA exposure, generating the same free BPA concentration in plasma than a 24 h-averaged oral exposure at the t-TDI (4 μg BPA/kg bw)		Corresponding estimated total BPA steady-state concentration in urine (μg/L)	
% of oral exposure	% of dermal exposure	Adult (70 kg)	Child (19 kg)
90%	10%	215	134
80%	20%	191	119
70%	30%	165	105

than an oral intake of 4 μg/kg bw averaged over 24 h.

Given the strong uncertainties underlying the estimations of the relative contributions of the non-dietary sources of exposure to the total BPA exposure (EFSA, 2015), it was decided not to suggest any HBM-GV_{GenPop} related to fixed percentages of the oral and dermal routes contributions to the total BPA exposure.

4.4. Level of confidence attributed to the HBM-GV_{GenPop}

An overall level of confidence (LoC) is allocated to each derived HBM-GV within HBM4EU, in order to reflect the reliability of the values, which is largely depending on the input values. Therefore, the LoCs do not only reflect the reliability but at the same time the lack of data and knowledge and can thereby serve additionally for priority setting. The LoC has to be taken in mind when interpreting biomonitoring results especially when conducting risk assessments intended to decide on the implementations of subsequent risk management measures. The overall LoC is set based on single LoCs given for the following criteria underlying the derivation of the value: the substance' epidemiological and toxicological database; the selection of the critical effect and mode of action; the selection of the key study; the selection of the POD; and finally, the extrapolation and adjustment of the POD. The overall LoC for the derived BPA HBM-GV_{GenPop} was set to ***medium,*** considering the following single LoCs for all criteria:

A *medium* confidence level is given regarding the nature and quality of the BPA epidemiological and toxicological database: despite the fact that this database is tremendously broad, discrepancies in outcomes among and between studies, and in particular between standard toxicological guideline studies on one side and a large number of small scale *in vitro* and *in vivo* research or experimental studies on the other side, has often led to contradicting results.

A *low* confidence level is given regarding the selected critical endpoint and knowledge on the mode of action: after having used a weight of evidence approach to assess the evidence on hazards, EFSA used the endpoint "general toxicity" for risk characterisation. The alteration of the kidney weight in adult mice was selected as the critical endpoint for deriving the 2015 t-TDI. EFSA thereby recommended that mechanistic studies in the kidney had to be performed to determine the mode of action of BPA in this organ. Even if the effect observed on the mammary gland was considered as 'likely', analysis of the data revealed very large confidence intervals on the BMD (benchmark dose) estimated from the models used. Thus, this endpoint was not used for the derivation of the t-TDI. However, since then, recent scientific literature has provided additional indications of reproductive and developmental effects at doses of BPA below the NOAEL for general toxicity, but also neurological/neurodevelopmental/ neuroendocrine, immune-modulatory and metabolic effects (Heindel et al. 2020).

A *medium* confidence level is given regarding the selected key study and critical dose: the two-generation study in mice by Tyl et al. (2008), in which alteration of the mean relative kidney weight is observed, was selected as key study for setting the t-TDI which is underlying the HBM-GV_{GenPop} derivation. This study followed an Organisation for Economic Cooperation and Development (OECD) guideline protocol (TG 416, enhanced; OECD, 2001) and was conducted under OECD Good Laboratory Practice Principles. However, a benchmark response (BMR) of 10% was set in order to calculate the $BMDL_{10}$ related to the kidney effect in adult mice. According to EFSA recommendations on BMD modelling however, a default 5% BMR is recommended in modelling continuous data. Setting the BMR at 5% would have decreased the t-TDI value. Moreover, OECD test guidelines are sometimes not sensitive enough to capture effects related to endocrine-disrupting modes of action (Beronius et al. 2014; Vandenberg et al. 2019).

A *medium* confidence is given regarding the inter- and intraspecies extrapolations, exposure profile and duration: the t-TDI from EFSA already includes AFs accounting for the intra- and interspecies differences (10 and 2.5 respectively). Regarding the extrapolation from the external oral dose to the biomarker concentration, a human calibrated PBPK model was used to determine the total BPA in urine consistent with the 24 h-averaged t-TDI. This constitutes an added value compared to calculations performed with a mass-balance equation (which is equivalent to a simple toxicokinetic model). It has to be noticed however, that the PBPK model was adjusted to a set of HBM data on BPA obtained in adults. Thus, uncertainty exists regarding the proposed HBM-GV_{GenPop} for children, related to the possible BPA toxicokinetic differences between adults and children (be it for the oral or dermal exposure route) and also to the physiological parameters (e.g. the volume of the skin as fraction of the BW) considered for the model predictions. Possible sex-related toxicokinetic differences, for example regarding the capacity of the skin to absorb BPA, may also be considered as a source of uncertainty. In addition, the daily environmental exposure to BPA is likely to occur rather by peaks of exposure particularly considering the food intake pattern (Ye et al. 2011), while we assumed in our simulations that a dose equivalent to the t-TDI was given at a constant rate over 24 h. Thus, the influence of exposure peaks and blood free BPA concentration peaks on the toxicological activity of BPA should be further studied.

4.5. Perspective for setting an HBM-GV_{Worker}

No HBM-GV_{Worker} is here recommended for the control of the health risks related to BPA in the practice of occupational health.

A possibility to assess the level of exposure that is occurring for a worker at the workplace (and which is adding to the background exposure coming from the environment) consists in calculating the difference in total BPA in urine measured from pre- and post-shift samples collected on the first day of the working week.

In addition, the exposure reference value for adults that may be established for BPA under HBM4EU could be used to assess whether the exposure at the workplace is adequately controlled or not. An exposure reference value is a statistically derived value, usually based on the upper end of the biomarker concentrations distribution in individuals of the general population (aged 18–65 years in order to best compare with the working population). This type of value cannot be regarded as protecting from the onset of health effects. Nevertheless, it allows for comparison with HBM results of exposed workers. Where HBM results of workers exceed the exposure reference value for a substance, it may indicate that control of exposure is not adequate and under these circumstances, employers will need to look at current work practices to see how they can be improved to reduce exposure.

The most important absorption pathways for BPA at the workplace are likely the dermal and inhalation pathways, through which higher concentrations of free BPA in plasma is generated in comparison with oral intake of BPA. Therefore, the value of $13.6.10^{-3}$ μg/L for free BPA in plasma at the end of the working week and working shift may be relevant as HBM-GV_{Worker}, but only if analytical capacities complying with QA/QC requirements will allow for its measurement. Progress is underway and the number of laboratories capable of performing reliable quantifications of plasmatic free BPA low-levels will surely increase in the near future. Yet, this value, whose derivation is based on EFSA's HED approach, may also need revision according to EFSA's reassessment of the t-TDI value.

CRediT authorship contribution statement

Eva Ougier: Writing - original draft, Methodology. **Florence Zeman:** Software. **Jean-Philippe Antignac:** Critical revision of the article. **Christophe Rousselle:** Methodology. **Rosa Lange:** Critical revision of the article. **Marike Kolossa-Gehring:** Critical revision of the article. **Petra Apel:** Critical revision of the article.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgments

We would like to thank Céline Brochot from INERIS for having provided the PBPK model code developed by C. Karrer.

Funding

The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 733032 and received co-funding from the author's organizations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106563.

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