The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer

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International Journal of Hygiene and Environmental Health 234 (2021) 113722

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer

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ARTICLE INFO

Keywords:
Human biomonitoring
Phthalates
HBM4EU
Human biomonitoring guidance values (HBM-GV)
Risk assessment
Chemical policy

ABSTRACT

Ubiquitous use of plasticizers has led to a widespread internal exposure of the European population. Until today, metabolites are detected in almost every urine sample analysed. This raised the urgent need for a toxicological interpretation of the internal exposure levels. The European Human Biomonitoring Initiative (HBM4EU) contributes substantially to the knowledge on the actual exposure of European citizens to chemicals prioritised within HBM4EU, on their potential impact on health and on the interpretation of these data to improve policy making. On that account, human biomonitoring guidance values (HBM-GVs) are derived for the general population and the occupationally exposed population agreed at HBM4EU consortium level. These values can be used to assess phthalate exposure levels measured in HBM studies in a health risk assessment context. HBM-GVs were derived for five phthalates (DEHP, DnBP, DiBP, BBzP and DPHP) and for the non-phthalate substitute Hexamoll® DINCH. For the adult general population, the HBM-GVs for the specific metabolite(s) of the respective parent compounds in urine are the following: 0.5 mg/L for the sum of 5-oxo-MEHP and 5-OH-MEHP; 0.19 mg/L for MnBP, 0.23 mg/L for MiBP; 3 mg/L for MBzP; 0.5 mg/L for the sum of oxo-MPHP and OH-MPHP and 4.5 mg/L for the sum of OH-MINCH and cx-MINCH. The present paper further specifies HBM-GVs for children and for workers.

1. Introduction

Human Biomonitoring (HBM) has increasingly been established globally as an instrument to inform policy and citizens about the exposure of the general public to anthropogenic chemicals. The European Human Biomonitoring Initiative (HBM4EU) is a joint effort of 30 European countries, and the European Environment Agency, co-funded by the European Commission under Horizon 2020 with the goal to improve chemical safety. Many countries in Europe and worldwide already run HBM programs to monitor exposure levels of environmental chemicals, some of them on a regular basis (WHO, 2015). In Europe, these programs had previously worked independently of one another. As a result, comparability of the national HBM data is limited. HBM4EU has created a European network that improves knowledge for the European Union's environmental and chemical policy by harmonizing the planning and implementation of HBM studies, as well as sample and data analysis across national borders (Ganzleben et al., 2017). HBM4EU also aims to establish a sustainable Europe-wide HBM that provides comparable results tailored to directly feed into the development of European policies in the fields of health, environment and chemical safety to protect human health more effectively (David et al., 2020; HBM4EU Website).

The HBM4EU consortium identified 18 substances and substance groups, including phthalates and Hexamoll® DINCH, as of high priority to answer open policy relevant questions by targeted research. To interpret the results of HBM studies, up-to-date health-related assessment values are a useful tool. Such values (as HBM-I values from the German HBM Commission or biomonitoring equivalents (BE) by Summit Toxicology and Health Canada) have been applied in national HBM programs in the past (Angerer et al., 2011; Apel et al., 2017; Aylward et al., 2013; Ewers et al., 1999; Faure et al., 2020; German HBM Commission, 2007a, b, c, 2014a; St-Amand et al., 2014). In HBM4EU, a broad consented methodology for so-called HBM guidance values (HBM-GVs)

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https://doi.org/10.1016/j.ijheh.2021.113722
Received 27 November 2020; Received in revised form 17 February 2021; Accepted 18 February 2021
Available online 9 March 2021

Abbreviations

AF	Assessment Factor
AGD	Anogenital Distance
ANSES	FrenchAgency for Food, Environmental and Occupational Health and Safety
BE	Biomonitoring Equivalent
BBzP	Butyl benzyl phthalate (CAS No.: 85-68-7)
CAS No	Chemical Abstract Service Number
DEHP	Diethyl hexyl phthalate (CAS No.: 117-81-7)
DFG	German Research Foundation
DiBP	Diisobutyl phthalate (CAS No.: 84-69-5)
DiDP	Diisodecyl phthalate (CAS-No.: 26761-40-0/68515-49-1)
DiNP	Diisononyl phthalate (CAS-No.: 28553-12-0/68515-48-0)
DnBP	Di-n-butyl phthalate (CAS-No.: 84-74-2)
DNEL	Derived No Effect Level
DPHP	Bis(2-propylheptyl) phthalate (CAS-No.: 53306-54-0)
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
F1 generation	First Filial generation
F2 generation	Second Filial generation
F_{ue}	Fractional urinary excretion coefficient
GD	Gestational Day
HBM	Human Biomonitoring
HBM-I value	Human biomonitoring I value from the German HBM Commission
HBM4EU	The European Human Biomonitoring Initiative
HBM-GV	Human Biomonitoring Guidance Value
$HBM\text{-}GV_{GenPop}$	Human Biomonitoring Guidance Value for the general population
$HBM\text{-}GV_{Worker}$	Human Biomonitoring Guidance Value for workers
Hexamoll®	DINCH 1,2-Cyclohexane dicarboxylic acid diisononyl ester (CAS No.: 166412-78-8)
LoC	Level of Confidence
LO(A)EL	Lowest Observed (Adverse) Effect Level
MnBP	Mono-n-butyl phthalate (CAS-No.: 131-70-4)
NO(A)EL	No Observed (Adverse) Effect Level
PBTK	Physiologically-based toxicokinetic
POD	Point of Departure
RSD	Relative Standard Deviation
SCOEL	Scientific Committee on Occupational Exposure Limits
TDI	Tolerable Daily Intake
TRV	Toxicity Reference Value

was established. These values, derived from epidemiological or toxicological data, indicate the concentration of a compound or its metabolite(s) in a biological matrix (e.g. blood, urine) at/under which a health risk is not anticipated, according to current knowledge (Apel et al., 2020a). Used at the population level, they can not only help to refine the public health risk assessment by identifying exposures of potential concern, but also indicate potential regulatory priorities and the need for (additional) measures to reduce exposure. Within HBM4EU, a methodology has been elaborated on the derivation of these guidance values not only for the general population ($HBM\text{-}GV_{GenPop}$) but also for occupationally exposed adults ($HBM\text{-}GV_{Worker}$). $HBM\text{-}GV_{GenPop}$ are equivalent to the HBM-I values from the German HBM Commission and similar to the BE values introduced by Summit Toxicology (Apel et al., 2017; German HBM Commission, 2007a, b, 2014a; Hays and Aylward, 2009; Hays et al., 2008, 2007). The $HBM\text{-}GV_{Worker}$ are similar to the biological limit values derived by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) as well as by the former Scientific Committee on Occupational Exposure Limits (SCOEL) or also to the biological tolerance values (BAT) set by the Working Group on the Setting of Threshold Limit Values in Biological Material of the German Research Foundation (DFG) (ANSES, 2014; Apel et al., 2020a; Bolt and Thier, 2006; DFG, 2014).

Each HBM-GV derived within HBM4EU underwent a consultation process with national experts to ensure a high degree of both scientific integrity and acceptance (for more information please see Apel et al., 2020a). As HBM-GVs are set for exposure biomarker(s) levels in a biological matrix, they can be directly compared to exposure levels measured in HBM studies, if the same biomarker(s) are measured with comparable quality-assured analytical methods. They are thereby an easy-to-use tool for performing an integral health risk assessment (covering all known and unknown sources and routes of exposure), and are complementary to external health-based guidance values (e.g. Tolerable Daily Intake (TDI)) that usually focus on specific sources or exposure routes (e.g. food).

The regulation of reprotoxic phthalates resulted in a change in use and in the exposure pattern within the general population over time. Whereas the exposure levels of old, well-known phthalates (DEHP, DnBP, BBzP) have decreased, an increase in exposure levels of high molecular weight phthalates such as DiNP, DiDP and DPHP has been observed over the last two decades. The exposure levels of the non-phthalate substitute Hexamoll® DINCH have also increased in some European countries (Frederiksen et al., 2020; Gyllenhammar et al., 2017; Kasper-Sonnenberg et al., 2019; Koch et al., 2017; Schmidtkunz et al., 2019; Shu et al., 2018). Thus, the widespread use of phthalates and their substitute still leads to their ubiquitous presence in the environment (Przybylińska and Wyszkowski, 2016; Szewczyńska et al., 2020) and in humans. The frequency of detection of the phthalate metabolites mentioned ranges from over 80 up to 100% of all urine samples analysed (Apel et al., 2017, 2020b; Correia-Sá et al., 2018; Dewalque et al., 2014; Frederiksen et al., 2011; Hartmann et al., 2015; Husøy et al., 2019; Kasper-Sonnenberg et al., 2019; Katsikantami et al., 2016; Koch et al., 2017; Myridakis et al., 2016; Schoeters et al., 2017; Schütze et al, 2014, 2015; Schwedler et al., 2019, 2020). Therefore, it is still urgently needed not only to monitor plasticizers in the European population but also to be able to interpret these results to adopt measures at European scale.

With this paper, the published general methodology for deriving HBM-GVs (see Apel et al., 2020a) is implemented for phthalates and a substitute plasticizer. HBM-GVs agreed on within HBM4EU for DEHP, DiBP, DnBP, BBzP, DPHP and the substitute Hexamoll® DINCH are presented.

2. Methods

The methodological approaches applied to derive HBM-GVs for the general and for the occupationally exposed population are outlined in detail in the strategy paper to derive HBM-GVs (Apel et al., 2020a). The strategy paper underwent a consultation process within the HBM4EU consortium to include the expertise of scientists from HBM4EU partner countries. Briefly, the strategy comprises that a literature research on recent toxicological and epidemiological data is conducted to find a robust exposure-health relationship to derive an HBM-GV. If present and reliable, human data is preferred over animal data. If it is not possible to establish a relationship between the internal concentration of the substance of concern or its metabolite(s) and a selected critical health effect in human data, a toxicity reference value (TRV) established by acknowledged authorities or committees can be used to derive an HBM-GV by means of toxicokinetic extrapolation. If there is no TRV available, an HBM-GV can be derived based on a point of departure (POD) identified in an animal toxicity study. Here too, information on

the toxicokinetics of the substance of concern is needed to calculate the internal concentration for the exposure biomarker. Depending on the information that is available, an HBM-GV can be calculated by using a simple toxicokinetic model such as the mass balance approach or by using a more sophisticated physiologically-based toxicokinetic (PBTK) model assuming a steady-state exposure condition in any case. The general formula used for the derivation of an HBM-GV based on an established TRV or on a TRV-like value calculated from an animal POD for a single metabolite using a mass-balance equation is shown in Formula 1.

Formula 1. Mass balance equation for the derivation of an HBM-GV for a single exposure biomarker based on an established TRV or based on a TRV-like value (calculated from an animal POD by applying assessment factors to the selected animal POD)

$$\text{HBM} - \text{GV} = \frac{\text{TRV or TRV} - \text{like value} \cdot \left[\frac{(\text{MW Metabolite}) \cdot (\text{Fue Metabolite})}{\text{MW Parent compound}}\right]}{\text{average daily urinary flow rate adjusted to bw}}$$

TRV = toxicity reference value; MW = molecular weight; F_{ue} = fractional urinary excretion coefficient; bw = body weight. Average daily urinary flow rates adjusted to bodyweight of 0.03 and 0.02 L/kg bw/d for children and adults, respectively as proposed by the German HBM Commission were used. To address the underlying uncertainties in the data used for the HBM-GV derivation, an overall level of confidence (LoC) is attributed to each HBM-GV. The LoC is estimated to be "low", "medium" or "high". The overall LoC is obtained by combining single LoC associated with the following criteria: 1) nature and quality of the epidemiological and toxicological data; 2) choice of critical effect and mode of action; 3) choice of the key study; 4) selection of the critical dose; and 5) extrapolations across and within species (see Apel et al., 2020a). The LoC aims at pointing out the uncertainties underlying the HBM-GV, as well as providing guidance to prioritise research activities needed for removing those uncertainties. Where new evidence is available, the values should be revised, especially those with lower LoC. It is important to stress out that the LoC does not relate as such to the level of protection towards adverse effects conferred by the value (a value with a low LoC for example may have been derived considering very conservative default assumptions) (Apel et al., 2020a).

3. Results

In the following the main approach in deriving HBM-GVs for the general population and for workers is detailed using DnBP as exemplary case. Details on input data for the derivation of the HBM-GVs for each compound can be found in the supplementary material 1. All HBM-GVs derived for the general population are summarised in Table 1 and HBM-GVs to be used in an occupational setting are displayed in Table 2. A detailed report on the derivation of HBM-GVs for DEHP and Hexamoll® DINCH has been published previously in an HBM4EU Deliverable and can be found on the HBM4EU website (see Apel and Ougier, 2017).

3.1. Selection of biomarkers of exposure for Di-n-butyl phthalate, DnBP

To select suitable biomarkers of exposure for which an HBM-GV can be derived, the toxicokinetic information on DnBP was reviewed with the emphasis on human data. A toxicokinetic study on one human volunteer by Koch et al. (2012) showed that within 24 h most of the dose (5.38 mg of D4-labelled DnBP) was excreted as total MnBP (84%) in urine, whereas oxidized metabolites were excreted to a minor extent (approximately 8%) (Koch et al., 2012). Seckin et al. (2009) applied a total dose of 3.6 mg in form of a capsule to 17 volunteers (male and female; including 4 children) and determined that within 24 h, 78% of the dose (median) was excreted as total MnBP via urine (Seckin et al., 2009). Anderson et al. (2001) demonstrated in a human voluntary toxicokinetic study on eight individuals per dose group (single dose of 0, 225 or 510 μg) that within 24 h, a mean of 69% of the ingested DnBP (molar basis) was excreted in urine as total MnBP, which is well in line with the other studies mentioned. On average 73% of the high dose (n = 6; two sample were not usable) and 64% of the low dose (n = 7; one sample was lost) administered was excreted in urine. The relative standard deviations (RSD), which give an estimation on the inter-individual variations were relatively low with 28% and 29% for the high and low dose, respectively (Anderson et al., 2001). MnBP is selected as biomarker of exposure suitable for the HBM-GV derivation, as it is identified as most suitable biomarker for determining DnBP exposure within HBM4EU (see Thomson et al., 2017) and total MnBP is excreted in relevant quantities in urine after DnBP intake. It needs to be noted, that MnBP was also found in urine after exposure to BBzP, but only when high doses were administered and only to a minor extent (Anderson et al., 2001). The fractional urinary excretion coefficient (F_{ue}) is a crucial parameter for the HBM-GV derivation to predict the daily excretion rate of the biomarker. The F_{ue} is the share of the orally absorbed compound that is excreted in form of the respective biomarker. Anderson et al. (2001) determined the mean F_{ue} for MnBP over all participants and doses to be 0.69. Both, Seckin et al. (2009) and Anderson et al. (2001) investigated the metabolism of DnBP by including several volunteers. The study by Anderson (2001) was the only study in which two doses were tested and the inter-individual variance of the excretions was given. Additionally, the doses tested in the Anderson study were the lowest and thus are more realistic to the levels of exposure of the general population not receiving capsule medication. Therefore, the F_{ue} determined in the Anderson study is considered in the HBM-GV calculation.

3.2. Selection of the TRV or POD and calculation of the HBM-GV for DnBP

3.2.1. General population

A literature search of the toxicological and epidemiological database was performed to identify the most sensitive endpoint (i.e. critical effect) for DnBP. The epidemiological studies on DnBP did not allow for establishing a relationship between the internal biomarker concentration and the critical health effects. In line with the methodology for deriving HBM-GVs, the second option was explored: whether a TRV is available, adequate to derive an HBM-GV. In the Annex XV restriction report on four phthalates (ECHA, 2016), a derived no effect level (DNEL) of 0.0067 mg/kg bw/d was derived based on the LOAEL of 2 mg/kg bw/d for developmental toxicity observed in the oral toxicity study in rats by Lee et al. (2004). Critical effects were reduction of testicular spermatocyte development and mammary gland changes in the male adult offspring (ECHA, 2016; Lee et al., 2004). An overall assessment factor (AF) of 300 was applied to this LOAEL, accounting for inter- and intraspecies differences (AF of 10 each) and for the extrapolation from a LOAEL to a NOAEL (AF of 3) (ECHA, 2016). As a review of the literature revealed no new findings that would justify an update of this POD, the use of the derived DNEL is supported. Thus, the derivation of an $\text{HBM-GV}_{\text{GenPop}}$ for the single metabolite MnBP is based on this DNEL of 0.0067 mg/kg bw/d as the TRV. The HBM-GV was calculated according to Formula 1 by using the molecular weights of the parent compound DnBP and the monoester metabolite MnBP, its corresponding F_{ue} and the adjusted urinary flow rates for adults and children each. The resulting $\text{HBM-GV}_{\text{GenPop}}$ for DnBP is 0.12 mg/L and 0.19 mg/L for children and adults, respectively (see Table 1).

3.2.2. Working population

The exposure protocol for the underlying key study used in the HBM-GV derivation for the general population (Lee et al., 2004) does not correspond to an occupational exposure scenario that should occur for pregnant working women. The exposure period in the Lee et al. (2004) study lasted from gestational day (GD) 15 to the end of lactation on postnatal day (PND) 21 and thereby included perinatal exposure

conditions (Lee et al., 2004). Therefore, the HBM-GV_{Worker} for the selected biomarker of exposure (MnBP) is derived based on an animal POD, representing the third option in the HBM-GV derivation as outlined by Apel et al. (2020a). In the toxicity study conducted by Lehmann et al. (2004), rats were exposed from GD12 to GD19 (Lehmann et al., 2004). This *in utero* period of exposure, when extrapolated to humans, corresponds to the critical window of exposure for the male reproductive system, that is during the 1st trimester of pregnancy. The reduction of foetal testicular testosterone in combination with the reduction in the expression of key genes encoding proteins involved in cholesterol transport and steroidogenesis observed in this study is selected as critical effect for which a POD of 10 mg/kg bw/d was identified (Lehmann et al., 2004). As absorption of DnBP is assumed to be similar for both the inhalation and oral routes, the retrieved urinary total MnBP concentration (free and glucuronidated) is anticipated to be the same for both routes. For this reason, a route-to-route extrapolation is not deemed necessary. A total AF of 100 accounting for inter- and intraspecies differences is applied to the NOEL, resulting in a TRV-like value of 0.1 mg/kg bw/d. The DnBP HBM-GV_{Worker} relating to urinary MnBP is calculated by using Formula 1 and is 3 mg/L (see Table 2).

3.3. HBM-GVs derived for 5 phthalates and the substitute Hexamoll® DINCH for the general population and workers

HBM-GVs have been derived according to the overall methodology agreed upon at HBM4EU consortium level previously published by Apel et al. (2020a). HBM-GV_{GenPop} for children and adults including adolescents and HBM-GV_{Worker} are summarised in Tables 1 and 2, respectively. The key toxicokinetic, epidemiological and/or toxicological data underlying the calculation of these values can be found in supplementary material 1.

Table 1
Human biomonitoring guidance values for the general population (HBM-GV_{GenPop}) derived for selected phthalates and the substitute Hexamoll® DINCH.

Parent compound	Biomarker(s)	HBM-GV_{GenPop} in mg/L[a]	
		Children[b]	Adults incl. adolescents[c]
DEHP	5-oxo-MEHP + 5-OH-MEHP	0.34	0.5
	5-cx-MEPP + 5-OH-MEHP	0.38	0.57
DnBP	MnBP	0.12	0.19
DiBP	MiBP	0.16	0.23
BBzP	MBzP	2.0	3.0
DPHP	oxo-MPHP + OH-MPHP	0.33	0.5
	oxo-MPHP	0.19	0.29
	OH-MPHP	0.14	0.22
Hexamoll® DINCH	OH-MINCH + cx-MINCH	3.0	4.5

5-oxo-MEHP: mono(2-ethyl-5-oxohexyl)phthalate (CAS No.: 40321-98-0); **5-OH-MEHP**: mono(2-ethyl-5-hydroxyhexyl) phthalate (CAS No.: 40321-99-1); **5-cx-MEPP**: mono (5-carboxy-2-ethylpentyl) phthalate (CAS No.: 40809-41-4); **MnBP**: monobutyl phthalate (CAS No.: 131-70-4); **MiBP**: monoisobutyl phthalate (CAS No.: 30833-53-5); **MBzP**: monobenzyl phthalate (CAS No.: 2528-16-7); **oxo-MPHP**: mono(propyl-6-oxo-heptyl) phthalate*; **OH-MPHP**: hydroxy-mono-propylheptyl phthalate*; **OH-MINCH**: cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-iso-nonyl) ester*; **cx-MINCH**: cyclohexane-1,2-dicarboxylic acid-mono-(carboxy-iso-octyl) ester*. Please note, that deriving an HBM-GV_{GenPop} for the subgroup of children under 6 years of age is not appropriate, considering the lack of relevant toxicokinetic data.
*no CAS number available.
[a] Rounded value.
[b] Including children 6–13 years of age.
[c] Including women of child-bearing age.

Table 2
Human biomonitoring guidance values for the working population (HBM-GV_{Worker}) derived for selected phthalates.

Parent compound	Biomarker(s)	HBM-GV_{Worker} in mg/L[a]
		Adults[b]
DEHP	5-cx-MEPP	0.62
DnBP	MnBP	3
DiBP	MiBP	3.5
BBzP	MBzP	3
DPHP	oxo-MPHP + OH-MPHP	0.7
	oxo-MPHP	0.4
	OH-MPHP	0.3

5-cx-MEPP: mono (5-carboxy-2-ethylpentyl) phthalate (CAS No.: 40809-41-4); **MnBP**: monobutyl phthalate CAS No.: 131-70-4); **MiBP**: monoisobutyl phthalate (CAS No.: 30833-53-5); **MBzP**: monobenzyl phthalate (CAS No.: 2528-16-7); **oxo-MPHP**: mono(propyl-6-oxo-heptyl) phthalate*; **OH-MPHP**: hydroxy-mono-propylheptyl phthalate*.
*no CAS number available.
[a] Rounded value.
[b] Including women of child-bearing age.

3.4. Global levels of confidence (LoC) attributed to each HBM-GV

As indicated in Table 3 of the supplementary material 2, the overall LoC for the HBM-GVs set for DEHP, DnBP, BBzP and Hexamoll® DINCH were evaluated to be “medium”, and the overall LoC for the HBM-GVs for DiBP and DPHP were set to “low”. The specific uncertainties considered to assign these overall LoC to the derived HBM-GVs are discussed in detail in supplementary material 2.

The derivation of HBM-GV_{GenPop} for DEHP and Hexamoll® DINCH, as well as an HBM-GV_{Worker} for DEHP have been published in a Deliverable (Apel and Ougier, 2017). However, the LoC for some of the single criteria have been adapted in the meantime for DEHP and Hexamoll® DINCH to be consistent in the assessment of the different criteria. As a result, the overall LoC for the HBM-GV_{GenPop} for Hexamoll® DINCH and also the HBM-GV_{Worker} set for DEHP was changed from low to medium. For more details please see supplementary material 2.

4. Discussion

The HBM-GVs for five phthalates and the non-phthalate substitute Hexamoll® DINCH presented in this paper allow for a direct toxicological interpretation of measured exposure biomarker levels of these compounds in urine. They constitute an easy-to-use screening tool for scientists and risk assessors. They enable the assessment of the chemical burden of the general and the occupational population, prerequisite for the identification of regulatory and scientific needs and priorities. Health-based guidance values for the general population that refer to the internal concentration of a biomarker have been introduced in the past for some phthalates and Hexamoll® DINCH with the HBM-I values derived by the German HBM Commission (values exist for DEHP, DPHP and Hexamoll® DINCH) (German HBM Commission 2007c; 2014b; 2015; summarised in Apel et al., 2017) and the BE values by Hays and Aylward from Summit Toxicology (values exist for DEHP, BBzP, DiNP and DnBP) (Aylward et al., 2009a, 2009b; Hays et al., 2011). Although the derivation concepts for the HBM-GVs, HBM-I and BE values are comparable (Angerer et al., 2011), some of the already existing values differ from those presented here, as some values have been derived years ago and new information has become available.

For DEHP, previous values, either BE or HBM-I were already set a decade ago, in 2009 and 2007, respectively. Both, the German HBM Commission (HBM-I value of 0.3, 0.5 and 0.75 mg/L for women of child-bearing age, children and men aged 14 years and older as well as the rest of the general population, respectively) and Summit Toxicology (BE value of 0.66 mg/L) proposed values based on the TDI established by EFSA in 2005 (Aylward et al., 2009b; German HBM Commission,

2007c). As no new evidence has been identified that would justify a different starting point, the TDI from 2005 is retained as POD for deriving the HBM-GV_{GenPop}. However, these derivations are based on human toxicokinetic information from studies by Koch et al. (2004; 2005) in which only one male volunteer participated. For the derivation of an HBM-GV_{GenPop} for DEHP, current and more robust human toxicokinetic data were included in the calculation. The study of Anderson et al. (2011) included 20 human volunteers of both sexes and thereby providing a more robust data basis for the determination of an F_{ue}. Presented HBM-GV_{GenPop} are lower than the BE value and the HBM-I values, except for the HBM-I value of 0.3 mg/L exclusively set for women of child-bearing age (German HBM Commission, 2007c). Please note, that the BE value for DEHP is set for the sum of 3 metabolites, MEHP, 5-OH- and 5-oxo-MEHP, whereas the HBM-GV_{GenPop} referred to here are set for the sum of two metabolite combinations each (5-OH-MEHP & 5-oxo-MEHP; 5-OH-MEHP & 5-cx-MEPP; see Table 1).

Similarly, new toxicokinetic information became available for DPHP, for which the German HBM Commission derived HBM-I values in 2015 (German HBM Commission, 2015). The F_{ue} used to extrapolate the concentration of the metabolites in urine corresponding to the TRV-like value of the parent compound was based on the study by Leng et al. (2014) (F_{ue} of 10.7% for OH-MPHP and 13.5% for oxo-MPHP after 48 h). Klein et al. (2018) obtained a F_{ue} about a factor of 4 lower (F_{ue} of 2.3% for OH-MPHP and 3.6% for oxo-MPHP after 46 h) than in the study by Leng at al. (2014). As the laboratory that performed the analysis and the analytical method were the same and similar doses were administered, both results were evaluated as equally reliable. Average F_{ue} of 5.97% for OH-MPHP and 7.95% for oxo-MPHP after ~24 h were calculated from the F_{ue} values indicated in the two studies (at 24 h for Leng et al., 2014 and 22 h for Klein et al., 2018) and used for the HBM-GV_{GenPop} derivation. Furthermore, the POD selected for deriving an HBM-GV_{GenPop} was different from the one chosen by the German HBM Commission for deriving an HBM-I value (German HBM Commission, 2015). In the present paper, the derivation is based on a TRV, i.e. the RfD of 0.1 mg/kg bw/d calculated by Bhat et al. (2014), who have considered effects on the thyroid (follicular hypertrophy/hyperplasia) observed in F1 adults in a two-generation feeding study (BASF, 2009). The German HBM Commission based their HBM-I values of 1 and 1.5 mg/L (sum of OH- and oxo-MPHP), for children and adults respectively, on a NOAEL of 40 mg/kg bw/d determined in a subchronic feeding study (BASF, 1995), in which effects on the thyroid and pituitary gland were considered critical. As a result, the HBM-GV_{GenPop} presented here is lower than the HBM-I value.

For Hexamoll® DINCH, there are HBM-I values for children and adults, set in 2014 (German HBM Commission, 2014b), but no BE values. As no new toxicological evidence was identified, the HBM-GV_{GenPop} are at the same level as the HBM-I values.

In 2009, Aylward et al. presented BE values for DnBP and BBzP based, among others, on the TDIs set by EFSA in 2005 (Aylward et al., 2009a). The HBM-GV_{GenPop} for DnBP and BBzP presented in this paper were derived based on different PODs (and endpoint, respectively). Thus, the HBM-GVs differ from previously set BE values (0.2 and 12 mg/L for DnBP and BBzP, respectively). With regard to DnBP, the DNEL of 0.007 mg/kg bw/d set by ECHA (2012, 2016) is based on the LOAEL of 2 mg/kg bw/d observed in the study by Lee et al. (2004). ECHA applied an overall AF of 300, accounting for interspecies and intraspecies differences (each AF = 10) and for the LOAEL-NOAEL extrapolation (AF = 3) according to the ECHA R8 guidance. EFSA however, used an AF for the LOAEL-NOAEL extrapolation of 2 for setting the TDI (EFSA, 2005, 2019). For the HBM-GV_{GenPop} derivation, the approach of ECHA was followed (ECHA, 2012, 2017), resulting in a similar value of 0.19 mg/L for adults and a lower value for children with 0.12 mg/L compared to the BE value for DnBP.

In case of BBzP, the TDI set by EFSA, 2005 based on reduced AGD in F1 and F2 rat offspring was not used as POD for the HBM-GV_{GenPop} derivation, nor another TRV. Instead, the LO(A)ELs of 100 mg/kg bw/d for foetal testicular testosterone suppression observed in the study by Furr et al. (2014) and for reduced serum testosterone levels as well as reduced epididymal sperm count and motility in F1 adult rats after *in utero* exposure observed in the study by Ahmad et al. (2014) were identified as substantial (Ahmad et al., 2014; Furr et al., 2014). It needs to be noted, that within HBM4EU the significance of smaller changes in testosterone levels in the foetus and the resulting possibility of adverse outcomes was controversially discussed. Therefore, another endpoint besides foetal testosterone suppression was considered when the POD was selected (i.e. epididymal sperm changes). As a result, the HBM-GV for BBzP is more than one order of magnitude higher than the values for DEHP and DnBP. Considering similar potencies for anti-androgenic effects (Howdeshell et al., 2008), this value must be used with caution. Further toxicity studies for BBzP are needed to evaluate, whether critical effects not assessed so far (i.e. testicular and mammary histology; dysgenesis of external genitalia) are occurring at low-level exposure to BBzP. Compared to the BE value, the HBM-GV_{GenPop} of 3 mg/L for adults and 2 mg/L for children presented here are lower.

Lastly, neither HBM-I, nor BE values exist for DiBP, making the HBM-GV_{GenPop} for DiBP presented in this paper the first health-related guidance value referring to the internal concentration of its metabolite MiBP.

The HBM-GVs derived under HBM4EU underwent a consultation with national experts nominated by the partner countries and the EU Policy Board on an HBM4EU consortium level and have been mutually agreed upon (see Apel et al., 2020a). This ensures the acceptance of these values by the European partner institutions and a comparable assessment of HBM data gathered in this project and presumably beyond, contributing to a harmonised approach towards a joint improvement of European chemical policy. The adoption and implementation at EU level remain to be discussed by the responsible EU authorities.

The presented HBM-GVs are rather intended to be used for the interpretation of results from HBM studies reflecting exposure of the general population (or workers sub-populations). The interpretation of HBM results towards the risk for the occurrence of an adverse health effect is more complex at the individual level. On the one hand, urinary concentrations of an individual measured in HBM studies are assumed to be subject to large within-day variations due to physiological factors of that individual (hydration status). In addition, within-day variations in urine samples are likely to occur due to the short biological half-lives of the biomarkers of exposure (Aylward et al., 2009a, 2017; Hays and Aylward, 2009). Therefore, for the analysis of individual samples, 24 h urine collections instead of spot urine samples is recommended. However, on a population basis, spot and 24 h samples produce comparable results (Christensen et al., 2012). On the other hand, there are underlying uncertainties in the HBM-GV derivation itself. These include general assumptions made regarding typical values for urinary flow rates and the origin of urinary excretion fraction data. These data often originate from a small number of volunteers, mostly men, only and data on inter-individual variability (e.g. due to sex or age, genetic polymorphism) often lacks (Angerer et al., 2011; Aylward et al., 2009a). The HBM-GVs are of limited interpretability in regard to multiple individual and health-associated factors and this needs to be clearly communicated. Nevertheless, they are helpful in raising awareness towards the possible health risks of chemical exposure as long as information is well prepared for lay people and guidance is given.

The HBM-GVs have their limitations as they allow only a single substance risk assessment. Various phthalates are frequently detected in investigated populations all over Europe (Cullen et al., 2017; Dewalque et al., 2014; Frederiksen et al., 2020; Gyllenhammar et al., 2017; Hartmann et al., 2015; Husøy et al., 2019; Schwedler et al., 2020) and thus a widespread concurrent exposure to multiple phthalates is given. Phthalates that show similar anti-androgenic effects are assumed to share a common mode of action and can act in a dose-additive manner as shown in rats (Howdeshell et al., 2007, 2008; Rider et al., 2010). Therefore, a cumulative risk assessment is rather warranted to protect

the population from the adverse health effects arising from exposure to phthalates (Apel et al., 2020b; Kortenkamp and Koch, 2020). In order to close this gap, a proposal for a methodology using the HBM-GVs in a cumulative risk assessment for anti-androgenic phthalates within HBM4EU will be established.

5. Conclusion and perspective

The restrictions and regulations of reprotoxic phthalates in the EU have led to a change in their exposure patterns. The population's exposure to older, well-known and reprotoxic phthalates (DEHP, DnBP, BBzP) has decreased, while exposure inter alia to DPHP and the non-phthalate substitute Hexamoll® DINCH thought to be less harmful has increased (Apel et al., 2020b; Frederiksen et al., 2020; Gyllenhammar et al., 2017; Hartmann et al., 2015; Kasper-Sonnenberg et al., 2019; Schwedler et al., 2019). Exposure levels of the population to phthalates and Hexamoll® DINCH must be assessed to timely implement necessary reduction measures. Furthermore, the monitoring of restricted phthalates and their alternatives is warranted to evaluate the effectiveness of the regulations in place and adopt new regulations if necessary. The HBM-GVs for the six substances presented in this paper form the basis for a harmonised health risk assessment of the European population. These values will be used to perform single-substance risk assessments by comparison with aligned HBM datasets from across Europe generated under the HBM4EU project. Furthermore, it is currently explored how HBM-GVs can be used to perform risk assessments for chemical mixtures (e.g. mixture of phthalates) to evaluate real-life exposure scenarios.

In addition to the six HBM-GVs described in this paper, HBM-GVs have been derived for cadmium and bisphenol A (Lamkarkach et al., 2021; Ougier et al., publ. submitted). It is anticipated that further HBM-GVs will be derived for bisphenol S, aprotic solvents (n-methyl-2-pyrrolidone, n-ethyl-2-pyrrolidone, dimethylformamide, dimethylacetamide), mercury and selected pyrethroids.

HBM-GVs are a valuable tool for the evaluation of exposures in a health-risk assessment. They constitute a common basis for assessment and they are easy to use as they can directly be compared to HBM data. The HBM4EU project was the first initiative proposing HBM-GVs agreed upon in a broader European consensus. In addition, the LoC assigned to each derived HBM-GV highlight data gaps and thus can help to foster research activities for future HBM-related international initiatives.

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.

Acknowledgement and 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. The authors thank all other national and international experts that contributed to this work by reviewing the derivation proposals during the consultation rounds.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113722.

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