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Human biomonitoring guidance values (HBM-GVs) for priority substances under the HBM4EU initiative – New values derivation for deltamethrin and cyfluthrin and overall results

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ABSTRACT

The European Initiative HBM4EU aimed to further establish human biomonitoring across Europe as an important tool for determining population exposure to chemicals and as part of health-related risk assessments, thus making it applicable for policy advice. Not only should analytical methods and survey design be harmonized and quality assured, but also the evaluation of human biomonitoring data. For the health-related interpretation of the data within HBM4EU, a strategy for deriving health-based human biomonitoring guidance values (HBM-GVs) for both the general population and workers was agreed on. On this basis, HBM-GVs for exposure biomarkers of 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), phthalates (diethyl hexyl phthalate (DEHP), di-n-butyl phthalate (DnBP), diisobutyl phthalate (DiBP), butyl benzyl phthalate (BBzP), and bis-(2-propylheptyl) phthalate (DPHP)), bisphenols A and S, pyrethroids (deltamethrin and cyfluthrin), solvents (1-methyl-2-pyrrolidone (NMP), 1-ethylpyrrolidin-2-one (NEP), N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC)), the heavy metal cadmium and the mycotoxin deoxynivalenol (DON) were developed and assigned a level of confidence. The approach to HBM-GV derivations, results, and limitations in data interpretation with special focus on the pyrethroids are presented in this paper.

1. Introduction

Human biomonitoring (HBM) is the determination of human exposure to contaminants that are detectable in the body and is worldwide increasingly used in population studies to provide an overview of the body burden in the population in general or in specific population groups. HBM is a valuable control instrument with regard to regulatory success and an important tool for further policy advice (Ganzleben et al., 2017; Louro et al., 2019; Ubong et al., this issue). In addition, HBM can be used to meet the information needs of citizens on issues related to environmental health protection (Uhl et al., 2021). HBM also plays an important role in occupational settings by complementing air measurements with individual measurements in various human matrices (ANSES, 2014).

In 2017, the European Human Biomonitoring Initiative HBM4EU was launched with the aim of establishing a European network of research institutions involved in the standardized collection and analysis of HBM data, to improve the state of knowledge for environmental and chemicals policy in the European Union and to enable comparability of HBM results across Europe (Gilles et al., 2021; Esteban López et al., 2021).

After five and a half years, the HBM4EU initiative marked a major step forward in the EU-wide establishment, harmonization, and quality assurance of human biomonitoring. This includes not only common agreements on study design, sampling and sample storage, methods to identify and quantify chemicals and/or their metabolites in human biological material, but also the data analysis and interpretation of the measurements results (Govarts et al., this issue).

With regard to the health-related evaluation of HBM results, a joint procedure has been agreed upon for deriving human biomonitoring

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guidance values (HBM-GVs). These values represent benchmark levels relating to the internal concentration of chemicals in e.g. blood or urine and are a key element for health-based risk assessment (Apel et al., 2020b) as well as an easy-to-use tool for comparison with HBM results. The HBM-GVs for the general population (HBM-GV_{GenPop}) indicate the concentration of a compound or its metabolite(s) in a biological matrix (e.g. blood, urine) at and below which a health risk is not anticipated, according to current knowledge (Apel et al., 2020b). The interpretation of these guidance values corresponds to that of the HBM-I values of the German HBM Commission (Apel et al., 2017; HBM Commission of the German Environment Agency, 2007, 2014) and is similar to that of the biomonitoring equivalents (BE values) insofar as these refer to substances with an effect threshold. BE values refer to chemicals' concentrations in biological material consistent with existing external exposure guidance values and were introduced by the US-based consulting firm Summit Toxicology (Hays et al., 2007, 2008).

HBM-GVs were also derived for occupationally exposed adults (HBM-GV_{Worker}). These values each represent the concentration of a substance or its specific and sensitive metabolite(s) in human biological media which should protect workers who are regularly exposed to the substance in question for 8 h per day and 5 days per week during their working lives from the harmful effects of medium- and long-term exposure. The HBM-GV_{Worker} are similar to the biological limit values (BLV) 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 "Assessment Values in Biological Material" of the German Research Foundation (DFG) (ANSES, 2014; SCOEL, 2013; DFG, 2021; Apel et al., 2020b). However, by definition, HBM-GVs can only be derived for substances for which a concentration without effect (threshold concentration) can be specified.

The joint procedure to derive HBM-GVs is published in a strategy paper (Apel et al., 2020b) that underwent - as well as each HBM-GV derivation - a consultation process within the HBM4EU consortium to include the expertise of scientists from HBM4EU partner countries.

Eighteen substances and substance groups were identified by the HBM4EU partner countries and EU institutions as of high priority because open policy relevant questions still had to be answered by targeted research (Ougier et al., 2021b). Corresponding biomarkers of exposure, the biological material to be analysed and analytical methods for the detection of the biomarkers of exposure for substances of the 1st and 2nd prioritisation round were compiled (Vorkamp et al., 2021; Esteban López et al., 2021) and formed the basis for further research activities. HBM-GVs were derived for some of the priority substances and used for subsequent health-related assessments of HBM studies. For some substances, only an HBM-GV for the general population or only for workers was proposed. This is partly due to the fact that, for example, exposure scenarios and results do not allow the derivation of HBM-GVs for workers (BPA) or no significant exposure is expected for the respective population (N,N-dimethylacetamide (DMAC) exposure of the general population). For a general overview, all derived values are presented in summary form, while the derivation of HBM-GVs for the pyrethroids is presented in more detail and for the first time.

2. Methods

The HBM-GVs were derived according to a systematic approach commonly agreed on within HBM4EU (Apel et al., 2020b). In short, a stepwise procedure is foreseen in which the existing literature on recent toxicological and epidemiological data on selected substances is reviewed and assessed for scope, quality, and relevance for the derivation of HBM-GVs. The first step consists in the selection of the most relevant biomarker(s). A biomarker is defined as any substance, structure or process that can be measured in the body or its degradation product(s) which influence(s) or predict(s) the incidence of outcome or disease. Biomarkers can be classified into biomarkers of exposure (BME), biomarkers of effects or biomarkers of susceptibility (Apel et al., 2020b). They are selected for the derivation of HBM-GVs according to defined criteria: specificity, sensitivity, half-life, availability of a suitable analytical method, invasiveness of biological sampling, and background level. The derivation of HBM-GVs for the selected biomarkers can then be conducted according to three possible options (Fig. 1). The most robust derivation and thus the 1st option is based on a relationship between human internal biomarker concentrations and adverse health effects. If those human data are unavailable, insufficient, or not reliable, it can be tried to proceed according to the 2nd option by converting existing external toxicity reference values (TRV), such as a Tolerable Daily Intake (TDI), or Occupational Exposure Limits (OEL), set by EU or relevant non-EU bodies, into internal values using toxicokinetic data or correlation equations based on a relationship between exposure and internal concentration. As a 3rd option, if the TRV is considered inappropriate or no TRV is available, an HBM-GV can be derived based on a point of departure (POD) identified in an experimental (animal) study. Uncertainty factors, also called assessment factors, are used depending on the respective data situation. A level of confidence (low, medium or high) is attributed to each calculated HBM-GV. The level of confidence should reflect the uncertainties identified during the derivation of the value and can be a good incentive to later revise values with estimated 'lower' level of confidence. In the following the derived values are shown depending on the derivation path. For the workplace, it is also indicated when it is best to sample so that a meaningful comparison can be made with the HBM-GV_{Worker}.

3. Results

3.1. First option: HBM-GVs based on a relationship between human internal biomarker concentrations and adverse health effects

As part of the HBM4EU work, HBM-GVs were derived in accordance with option 1 for two substances: Cadmium and its compounds and N-Dimethylformamide (DMF).

3.1.1. Cadmium and its compounds

The heavy metal Cadmium (Cd) is an environmental pollutant that occurs naturally and is also released from industrial and agricultural activities. Foodstuffs are the main source of cadmium exposure for the non-smoking general population. Urinary Cd (U–Cd) is a well-known and reliable indicator of long-term exposure to Cd for the general population as well as for occupationally exposed adults. Blood Cd (B–Cd) is a useful indicator of Cd-exposure during the last months (3–6 months). Therefore, B–Cd is a useful biomarker to monitor Cd occupational exposure in addition to U–Cd, especially for new employees at the workplace. There is ample evidence of nephrotoxicity as critical effect in the case of exposure to cadmium and quantitative relationships between the concentration of Cd both in urine (U–Cd) and in blood (B–Cd) and renal dysfunction in workers and in occupationally unexposed persons are available (EFSA, 2009; ANSES, 2018). Tubular and glomerular renal effects have been observed with the former being better characterized. A comprehensive literature review by Lamkarkach et al. (2021) on effects suspected to be related to Cd exposure showed also bone and cardiovascular effects for low cumulated exposure as indicated by U–Cd and/or B–Cd. However, for the time being, these effects were not selected as critical effects for the derivation of HBM-GVs, as the weight of evidence was not considered sufficient within the HBM4EU project (Lamkarkach et al., 2021). Based on a robust meta-analysis conducted by EFSA (2009) on cadmium-related elevated levels of beta-2-microglobulin (β2M) in urine as a marker of low molecular weight proteinuria, an HBM-GV_{GenPop} for U–Cd of 1 μg/g creatinine (creat) is recommended for adults older than 50 years. Taking into account the accumulation of Cd in the human body throughout life, threshold or 'alert' values according to age were estimated for U–Cd

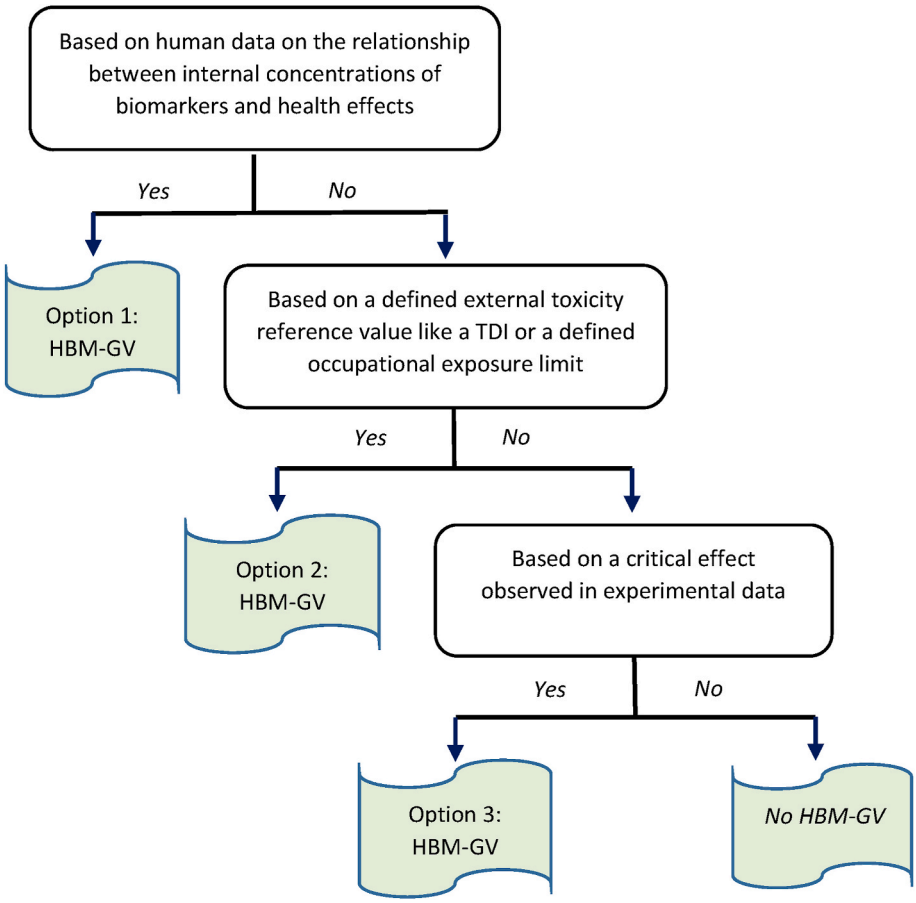

Fig. 1. Decision tree for determining HBM-GVs (taken from Lamkarkach et al., 2022, slightly modified).

according to the physiologically based pharmacokinetic (PBPK) model by ANSES (2018). These values referring to age groups represent a further specification and improvement of the HBM-I values earlier proposed by the German Human Biomonitoring Commission (HBM Commission of the German Environment Agency, 2011) (Lamkarkach et al., 2021). For the workplace, an HBM-GV_{Worker} of 2 μg/g creat was derived from the study of Chaumont et al. (2011) for U–Cd, and additionally an HBM-GV_{Worker} for B–Cd of 5 μg/L was proposed based on the recommendation of the American Conference of Governmental Industrial Hygienists (ACGIH, 2016). Both HBM-GV_{Worker} refer to renal effects. The HBM-GV_{Worker} for U–Cd is in line with the biological limit value (BLV) set by the amendment of the European Carcinogens and Mutagens Directive (EU) 2019/983 of the European Parliament and of the Council in June 2019 (2 μg/g creat for U–Cd) (Lamkarkach et al., 2021). This BLV is based on renal effects and the European Scientific Committee on Occupational Exposure Limits (SCOEL) recommendation.

Table 1
Derivation of HBM-GVs according to option 1, based on a relationship between human internal biomarker concentrations and adverse health effects.

Substance/ Exposure biomarker	Critical effect	Key studies and Point of departure (POD)	Assessment factor	HBM-GV_{GenPop}	HBM-GV_{Worker}	Level of confidence (LoC)
Cadmium/U–Cd	Nephrotoxicity	BMD_5L_{95}: 4 μg/g creat from meta-analysis of 35 studies (EFSA, 2009)	Intra-species variation (Chemical-specific "adjustment factor") = 3.9	In μg/g creat >50 years (y): 1 41–50 y: 0.8 31–40 y: 0.5 21–30 y: 0.3 11–20 y: 0.2 ≤ 10 y: 0.1 (PBPK model by ANSES, 2018)		High
		Chaumont et al. (2011)	Intraspecies variation = 3 (average age 45 y)		2 μg/g creat	High-medium
Cadmium/B–Cd	Nephrotoxicity	BEI: 5 μg/L (ACGIH, 2016)		n.d.	5 μg/L	High-medium
DMF/tNMF	Hepatotoxicity	Several studies carried out at workplace		n.d.	10 mg/L (or 10 mg/g creat)	High
DMF/AMCC	Hepatotoxicity	Several studies carried out at workplace		1 mg/g creat[a]	10 mg/g creat	Medium-low

U–Cd: Urinary Cadmium, B–Cd: Blood Cadmium, tNMF: total N-methylformamide, AMCC: N-acetyl-S-(N-methylcarbamoyl)cysteine.
[a] Provisional value without consultation of HBM4EU partners.

Cadmium is considered a genotoxic carcinogen, causing, among other effects, oxidative DNA damage, inhibition of DNA repair, and deregulation of cell proliferation, with a threshold level for these effects below which no effect is expected (ECHA, 2020c). But it is not possible to establish exposure risks on the basis of Cd's carcinogenicity due to a lack of a consistent relationship in epidemiological studies and the complex interactions with smoking and other co-carcinogenic factors.

The level of confidence attributed to the HBM-GV for the general population is 'high'. For the working population, the levels of confidence attributed to the U–Cd and B–Cd HBM-GVs are 'high-medium' (Lamkarkach et al., 2021).

The essential information for the derivation of, and the numerical values for the HBM-GVs for the general population and workers are summarized in Table 1.

3.1.2. N-dimethylformamide (DMF)

Release to the environment of the solvent N-dimethylformamide (DMF) can occur from industrial use e.g. in processing aids and from application of products like machine wash liquids/detergents, automotive care products, paints and coatings or adhesives, fragrances and air fresheners (ECHA substance infocard). Exposure to DMF in the workplace can occur through both inhalation and dermal contact. Results on DMF biomonitoring show sufficient and robust relationships between health effects (i.e. hepatic effects, antabuse effects, or effects on the gastrointestinal tract) and levels of biomarkers of exposure, mainly total N-methylformamide (tNMF), which is the sum of N-hydroxymethyl-N-methylformamide and N-methylformamide, and N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in urine. These BME were identified as the most appropriate and rather complementary BME for the derivation of HBM-GV_{Worker} (Lamkarkach et al., 2022). Liver damage which is reflected by an elevation of serum hepatic enzymes activity proved to be the critical effect for the derivation of the HBM-GV_{Worker}. Of the studies conducted in the workplace, four were assessed as suitable for deriving an HBM-GV_{Worker} (Sakai et al., 1995; He et al., 2010; Kilo et al., 2016; Wu et al., 2017) and based on these, an HBM-GV_{Worker} of 10 mg tNMF/L (or 10 mg/g creat) was agreed on (Lamkarkach et al., 2022). This value is slightly lower than the values previously proposed by SCOEL (2006), ACGIH (2017) or DFG (2019) (15 mg/L to 30 mg/L). The reasons for this are, on the one hand, the approach used, SCOEL and DFG established the values for tNMF in urine based on the occupational exposure limit (OEL) for DMF and correlations between external exposure and the concentration of biomarker in urine. This is not the best choice as DMF is readily absorbed through the skin. On the other hand, ACGIH has retained option 1, which builds on relationships between internal biomarker concentration and health effects, but has not taken into account the most recent publications by Kilo et al. (2016) and Wu et al. (2017), which were identified by Lamkarkach et al., (2022) as important for deriving the HBM-GV_{Worker}. Considering tNMF half-life time, end-of-shift urine sampling at any day of the workweek can be performed for this biomarker. Complementing the value for tNMF as most reliable biomarker of exposure, an HBM-GV_{Worker} for AMCC was derived by Lamkarkach et al. (2022), which is an indicator of cumulative exposure after several days. The basis was the same four studies which were used for the elaboration of an HBM-GV_{Worker} for tNMF. Due to the wide range of NOAEL values and the large margin between NOAEL and LOAEL values, a conservative limit value of 10 mg/g creat AMCC was agreed on and is provisionally recommended. As DMF LOAEL and NOAEL for developmental effects in the most sensitive species are higher than the corresponding values for hepatotoxic effects, the HBM-GV_{Worker} for tNMF and AMCC which were established to protect against hepatotoxic effects are expected to also protect from developmental toxicity. Further, as DMF carcinogenic effects in animals follow hepatic damage, as there is no sufficient evidence of DMF genotoxicity, and the three reported clusters of testis cancer do not constitute a sufficient evidence of DMF carcinogenicity in humans, the HBM-GV_{Worker} for tNMF and AMCC are expected to also protect from carcinogenic effects (Lamkarkach et al., 2022). Alcohol intolerance can be observed at lower exposure levels in some individuals, therefore workers exposed to DMF should be informed about the risk of alcohol consumption. On the other hand, acute and chronic alcohol consumption interferes with DMF metabolism and tNMF and AMCC elimination kinetics; thus, information on alcohol habits and alcohol consumption should be collected to allow interpretation of the measurement results (Lamkarkach et al., 2022). The levels of confidence attributed by Lamkarkach et al. (2022) to the HBM-GV_{Worker} are set to 'high' for tNMF and 'medium-low' for AMCC. For the purpose of risk assessment, the HBM-GV_{Worker} for AMCC of 10 mg/g creat was used by Mahiout et al. (2022) and divided by another assessment factor of 10 to consider more sensitive subgroups of the population, resulting in a provisional HBM-GV_{GenPop} of 1 mg/g creat for the DMF metabolite AMCC (Mahiout and Santonen, 2022). The essential information for the derivation of HBM-GVs, and the numerical values for the HBM-GVs for workers and the general population are summarized in Table 1.

3.2. Second option: HBM-GVs based on toxicity reference values (TRV) like TDI

As part of the HBM4EU work, HBM-GVs were derived in accordance with option 2 for nine substances: deltamethrin, cyfluthrin, diethyl hexyl phthalate (DEHP), di-n-butyl phthalate (DnBP), diisobutyl phthalate (DiBP), bis-(2-propylheptyl) phthalate (DPHP), 1,2-Cyclohexane dicarboxylic acid diisononyl ester (DINCH), bisphenol A (BPA), and deoxynivalenol (DON). The HBM-GVs derived are for the general population, information on their derivation and the numerical values for the HBM-GVs are summarised in Table 2. The derivation of the HBM-GVs for deltamethrin and cyfluthrin is described in more detail in the present article.

3.2.1. Pyrethroids

3.2.1.1. Deltamethrin. Deltamethrin ((S)-α-cyano-3-phenoxybenzyl (1R, 3R)- 3 -(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate) is a synthetic pyrethroid that is currently registered in the European Union as a biocide (product group 18: insecticides, acaricides, and products to control other arthropods) and as an active substance in plant protection products (ECHA, 2011a; EU pesticides-database). The name refers to cis-deltamethrin as the active isomer; other isomers are considered to be impurities (EC, 2018b). Exposure of the general population to deltamethrin occurs primarily through residues in food. From animal experiments and human examinations, it is known that following oral intake, deltamethrin is rapidly absorbed and a significant proportion is already metabolized in the gastrointestinal tract and thus no longer bioavailable. Via hydrolysis of the ester bond, which results in substantial detoxification, the metabolism leads to the formation of DBCA (3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanoic acid) and 3-PBA (3-phenoxybenzoic acid) (EC, 2018b). While 3-PBA is also formed by the metabolism of pyrethroids other than deltamethrin, DBCA represents a deltamethrin-specific metabolite (Schettgen et al., 2002).

The excretion of deltamethrin was studied by Sams and Jones (2012) in a small group of five volunteers (3 males + 2 females, age 23–55 years old, weight 77–107 kg) who received a single oral dose of 0.01 mg/kg bw/d dissolved in ethanol and diluted in a soft drink. Total urine was collected within 0–60 h after intake at time intervals of initially 2 h and after 8 h at longer intervals. The volume of each sample was recorded and creatinine was determined to adjust for dilution. Urine samples were heated for 2 h after addition of sulphuric acid to hydrolyse any conjugates, were then extracted with chlorobutane and analysed by gas chromatography-mass spectrometry (GC-MS) for the two metabolites, DBCA and 3-PBA. The limit of detection (LoD) for both metabolites was 1 μg/L. Elimination of both metabolites was rapid with mean half-lives of 3.6 h (DBCA) and 7.1 h (3-PBA). The mean recovery of DBCA in urine

Table 2
Derivation of HBM-GVs according to option 2, based on an existing TRV.

Substance/Exposure biomarker/Biological material	Critical effect	Toxicity Reference Value (TRV) [mg/kg bw/d]	Toxico-kinetics	HBM-GV_{GenPop} [mg/L urine]	Level of confidence
Deltamethrin/DBCA/urine	Lowered body weight, behavioural changes, and clinical signs of neurotoxiciy	ADI: 0.01 Studies: 90 d, rats; 90 d dogs; 1-year dogs (ECHA, 2011a; EC, 2018b)	Mass balance approach, Fue: 0.45 (Sams and Jones, 2012)	Children: 0.09 Adults: 0.13	Medium
Cyfluthrin/FPBA/urine	Acute neurotoxicity	ADI: 0.01 4-week rat study with β-cyfluthrin (EC, 2017a; EC, 2017b; EC, 2020; EFSA, 2020)	Mass balance approach, Fue: 0.47 (Leng et al., 1997a; Hays et al., 2009)	Children: 0.08 Adults: 0.13	Medium
DEHP/5-oxo-MEHP + 5-OH-MEHP/urine DEHP/5-cx-MEPP + 5-OH-MEHP/urine	Impairment of testicular development	TDI: 0.05 (EFSA, 2005a)	Mass balance approach, 5-OH-MEHP, $Fue_{(48h/24h)}$: 0.156/0.149; 5-oxo-MEHP, $Fue_{(48h/24h)}$: 0.113/0.109; 5-cx-MEPP, $Fue_{(48h/24h)}$: 0.139/0.132 (Anderson et al., 2011)	Children: 0.34 Adults: 0.5 Children: 0.38 Adults: 0.57	Medium
DnBP/MnBP/urine	Delayed germ cell development and male mammary gland changes after exposure from GD 15 to PND 21	DNEL: 0.0067 (ECHA, 2016)	Mass balance approach, $Fue_{(24h)}$: 0.69 Anderson et al. (2001)	Children: 0.12 Adults: 0.19	Medium
DiBP/MiBP/urine	Delayed germ cell development and male mammary gland changes after exposure from GD 15 to PND 21	DNEL: 0.0083 (ECHA, 2016) Read across with DnBP considering 25% potency difference (Saillenfait et al., 2008)	Mass balance approach, $Fue_{(24h)}$: 0.7 Koch et al. (2012)	Children: 0.16 Adults: 0.23	Low
DPHP/oxo-MPHP + OH-MPHP/urine DPHP/oxo-MPHP/urine DPHP/OH-MPHP/urine	Thyroid follicular hypertrophy/hyperplasia observed in F1 adult rats	RfD: 0.1 (Bhat et al., 2014)	Mass balance approach,oxo-MPHP, $Fue_{(\sim 24h)}$: 0.0795; OH-MPHP, $Fue_{(\sim 24h)}$: 0.0597 (averaged values: Leng et al., 2014 & Klein et al., 2018)	Children: 0.33 Adults: 0.5 Children: 0.19 Adults: 0.29 Children: 0.14 Adults: 0.22	Low
Hexamoll® DINCH/OH-MINCH + cx-MINCH/urine	Nephrotoxicity	TDI: 1 (EFSA, 2006)	Mass balance approach, OH-MINCH, $Fue_{(48h/24h)}$: 0.1073/0.0955; cx-MINCH, $Fue_{(48h/24h)}$: 0.0203/0.0167 (Schütze et al., 2017)	Children: 3 Adults 4.5	Medium
BPA/total BPA/urine	Increased relative mean kidney weight	t-TDI: 0.004 (EFSA, 2015)	TK model by Karrer et al. (2018)	Children: 0.135 Adults: 0.230	Medium
DON/total DON/urine	Reduced body weight gain	group-TDI for DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside: 0.001 (EFSA, 2017)	TK model by Mengelers et al. (2019)	0.023 (CI: 0.005–0.033) Based on a 24-h urine sample	Medium

HBM-GV_{GenPop}: Human biomonitoring guidance value for the general population; DBCA: 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanoic acid; FPBA: 4 fluoro-3-phenoxybenzoic acid; DEHP: diethyl hexyl phthalate; 5-oxo-MEHP: mono(2-ethyl-5-oxohexyl)phthalate; 5-OH-MEHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; 5-cx-MEPP: mono (5-carboxy-2-ethylpentyl) phthalate; DINCH: 1,2-Cyclohexane dicarboxylic acid diisononyl ester; OH-MINCH: cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-iso-nonyl) ester; cx-MINCH: cyclohexane-1,2-dicarboxylic acid-mono-(carboxy-iso-octyl) ester; DnBP: di-n-butyl phthalate; MnBP: monobutyl phthalate; DiBP: diisobutyl phthalate; MiBP: monoisobutyl phthalate; DPHP: bis-(2-propylheptyl) phthalate; oxo-MPHP: mono(propyl-6-oxo-heptyl) phthalate; OH-MPHP: hydroxy-mono-propylheptyl phthalate; BPA: bisphenol A; DON: deoxynivalenol; F_{ue}: fractional urinary excretion coefficient or urinary excretion factor; TRV: toxicity reference value; bw: body weight; TDI: tolerable daily intake; t-TDI: temporary tolerable daily intake; ADI: acceptable daily intake; RfD: reference dose; DNEL: derived no effect level; TK: toxicokinetic; CI: confidence interval.

as a proportion of the administered dose over the initial 24 h post-dose was 45% (range 18–64%). This value was practically unchanged when taking into account a 48 h collection period (46%, range 19–66%). DBCA was excreted almost twice as rapid as 3-PBA. Also, the level of DBCA in urine was within the first 24 h about five times higher than that of 3-PBA: The mean level of DBCA in 24-h total urine reached 58.3 (range: 42.2–86.7) μmol/mol creat, while that of 3-PBA only reached 11.9 (range 8.0–18.5) μmol/mol creat. Adjusting for a 70 kg bw individual, these values result in 42.8 μmol DBCA/mol creat and 8.7 μmol 3-PBA/mol creat, respectively. The fact that both metabolites were not excreted in equimolar amounts in urine as expected from the molecular structure may be explained by further formation of 4-hydroxy-3-PBA (Sams and Jones, 2012). It is clear from the above that the urinary excretion rate of the specific metabolite DBCA within 24 h is high

enough to use DBCA as a biomarker for deltamethrin exposure, and hereby also to calculate an HBM-GV. Besides the method published by Sams and Jones (2012), there are even more sensitive methods for the determination of DBCA, for example the highly sensitive and specific gas chromatography-tandem mass spectrometry (GC/MS/MS) -method to simultaneously quantify the metabolites of the most common synthetic pyrethroids in urine, described by Schettgen et al. (2016) with a limit of quantification for DBCA of 0.01 μg/L urine.

A Tier II Epidemiology Report focused on non-carcinogenic and carcinogenic health effects in humans for the chemical class of pyrethroids, as well as selected individual pyrethroids including deltamethrin was compiled by the U.S. EPA (2019a). A total of 62 published epidemiological studies was reviewed. Studies regarding non-carcinogenic effects included neurodevelopmental, neurobehavioral and neurocognitive effects, birth defects, male reproductive effects with respect to semen quality, male reproductive hormone levels, sperm damage/genetic abnormalities and other effects like coronary heart disease in adults, respiratory effects, autism spectrum disorders (ASD) in children, thyroid hormone levels in neonates. Based on this review, there is - according to U.S. EPA (2019a) - no or insufficient evidence to suggest a clear associative or causal relationship between exposure to pyrethroid pesticides and the non-carcinogenic health outcomes examined. A quality-based review of pyrethroid epidemiology further concluded that pyrethroids as a group are unlikely to adversely affect human fertility or reproductive capability (Burns and Pastoor, 2018). Regarding carcinogenic effects, the U.S. EPA concluded that "for childhood brain tumors and childhood leukemia, there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship with pyrethroid exposures." Furthermore, "there is no evidence at this time to conclude that there is a clear associative or causal relationship between pyrethroid exposure and breast cancer" (US EPA, 2019a). Many of the published studies were found to be of low quality because they were designed as cross-sectional studies, rather than cohort or case-control studies in which temporal aspects are taken into account.

An acceptable daily intake (ADI) value for deltamethrin of 0.01 mg/kg bw/d was derived in 2000 by the Joint Meeting of the Food and Agriculture Organization (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group (JMPR, 2000), based on a NOAEL of 1 mg/kg bw/d in one-year and two-year oral studies with dogs and a two-year oral study with rats using an overall assessment factor of 100. This default uncertainty factor for inter- and intra-species extrapolations in pyrethroids risk assessment is also still recommended by the U.S. EPA (2019b). ECHA and EFSA assessments came, based on results of two dog studies (90 days and one-year) and one rat study (90 days) to the same numerical value for the ADI as JMPR (ECHA, 2011a; EC, 2018b). The value is current and the literature search did not reveal any new findings on the effects of deltamethrin to question this value. The data base is broad: repeated dose toxicity studies, mostly with oral administration of deltamethrin, were conducted with rats, mice, and dogs. A NOAEL of 1 mg/kg bw/d was obtained in a subchronic feeding study with rats, based on non-specific effects (lowered body weight) at the next higher dose. An identical NOAEL of 1 mg/kg bw/d and a NOAEL of 1.1 mg/kg bw/d were also obtained in chronic toxicity studies with rats, based on lower body weight gain and hepatic changes, respectively. Studies with oral exposure of dogs to deltamethrin over 90 days or 1 year also delivered a NOAEL of 1 mg/kg bw/d, based on behavioural changes and clinical signs of neurotoxiciy at higher doses. In vitro and in vivo studies provided no evidence of genotoxicity of deltamethrin, and chronic toxicity/carcinogenicity studies with rats and mice provided no evidence of carcinogenicity. Also, no effects on fertility or development were observed or only observed at doses which already led to maternal toxicity. Furthermore, deltamethrin does not meet the World Health Organization (WHO) definition of an endocrine disruptor, that means it does not alter any function(s) of the endocrine system and does not cause any adverse health effects in this respect in an intact organism, its progeny, or (sub)- populations (WHO, 2012). A number of neurotoxicity studies with single or repeated exposure of adult animals to deltamethrin or with exposure during gestation and postnatal development are available. Studies with adult animals provided acute NOAEL or benchmark doses similar to those NOAEL obtained in studies with repeated exposure, e.g., a "threshold dose" of 0.99 mg/kg bw/d was derived for acute effects of deltamethrin on motor function in rats. Furthermore, the U.S. EPA concluded that the developmental neurotoxicity studies do not provide evidence for a higher sensitivity during development and that an additional assessment factor is not necessary (US EPA, 2019b). Thus, the ADI and, based on this, the HBM-GVs to be calculated in the following are also protective against acute neurotoxic effects (EC, 2018c).

The ADI (EC, 2018a, b; ECHA, 2011a; JMPR, 2000) as external toxicity reference value can be translated into a corresponding $\text{HBM-GV}_{\text{GenPop}}$ by using the following mass balance equation, assuming steady-state conditions:

$$\text{HBM-GV}_{\text{GenPop}} = \frac{\textbf{ADI} \bullet \left[\frac{\textbf{MW(DBCA)} \bullet \textbf{Fue(DBCA)}}{\textbf{MW(Deltamethrin)}}\right]}{\textbf{Daily urinary flow rate adjusted to the bw}}$$

Here is MW the molecular weight (DBCA: 298 g/mol, deltamethrin: 505.2 g/mol, ratio: 0.59) and Fue the molar excretion factor of 0.45 (Sams and Jones, 2012). Relating, in a simplified approach, the calculated excretion to the weight proportional amount of urine per day (0.03 L/kg bw/d for children and 0.02 L/kg bw/d for adults (Apel et al., 2020b), the ADI for deltamethrin corresponds to the following concentration of DBCA in urine:

Children: 0.01•0.59•0.45 mg/kg bw/d: 0.03 L/kg bw/d = 0.0885 mg DBCA/L urine

Adults: 0.01•0.59•0.45 mg/kg bw/d: 0.02 L/kg bw/d = 0.133 mg DBCA/L urine

On this basis, $\text{HBM-GV}_{\text{GenPop}}$ of 90.0 μg DBCA/L urine for children and 130 μg DBCA/L urine for adults were derived for the interpretation of biomonitoring results on deltamethrin in the general population. The level of confidence is rated medium.

For information and comparison, Aylward et al. have already derived urinary biomonitoring equivalents (BEs) in 2011 (Aylward et al., 2011). At the time this calculation was performed, no human data were available regarding the quantitative excretion of the deltamethrin-specific metabolite DBCA in urine. Instead, Aylward et al. (2011) used data from human toxicokinetic studies with cypermethrin, which differs from deltamethrin only in the halogen groups at the vinyl moiety (chlorine instead of bromine). Based on this read across, BE values of 50 μg DBCA/L (adults) and 7 μg/L (children) were derived consistent with the U.S. EPA reference dose (RfD). With reference to the ADI of 0.01 mg/kg bw/d, urinary BE values of 60 μg DBCA/L were derived for both children and adults (Aylward et al., 2011).

With the human toxicokinetic data of Sams and Jones (2012) it was now possible to propose updated HBM guidance values for the general population of 90 μg DBCA/L for children and 130 μg DBCA/L for adults.

3.2.1.2. Cyfluthrin. Cyfluthrin (IUPAC name, unspecified stereochemistry: (RS)-α-cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS; 1RS,3RS)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate) is a synthetic pyrethroid. The cyfluthrin molecule contains three chiral centers, giving rise to four enantiomeric pairs denoted as diastereomer I to IV. Technical cyfluthrin (thereafter referred to as "cyfluthrin") is a mixture of all four diastereomeric enantiomer pairs (i.e. eight isomers), which are present in the mixture in approximately equal proportions (about 20–35% of each). β-cyfluthrin is the common name for the mixture of enantiomer pairs II and IV in a ratio of about 1:2; the sum of the proportions of the other two pairs is less than 5%. The two diastereomeric

pairs II and IV of β-cyfluthrin represent the biologically active isomers of cyfluthrin. They are present in cyfluthrin at a concentration of about 40%. Cyfluthrin is currently approved in the European Union (and Switzerland) as an active substance for use in biocidal products of product-type 18 (insecticides, acaricides and products to control other arthropods) until 28/02/2028 (EC, 2016; ECHA Dissemination, 2021). For plant protection purposes in the EU, cyfluthrin and also β-cyfluthrin are no longer approved. The reasons put forward by EFSA for the non-renewal of approval for β-cyfluthrin as active substance in plant protection products were specifically because of unacceptable risks for workers loading and sowing beet seeds treated and for workers and operators using the respective plant protection products on tomatoes in greenhouses. Furthermore, in cases of β-cyfluthrin application to potato and wheat fields, high risks to residents have been identified. In addition, based on the available data, the consumer risk could not be conclusively assessed. Despite the non-approval of cyfluthrin and β-cyfluthrin as active substances in plant protection products in the EU, residues in imported food and feed cannot be excluded and this, like the use of cyfluthrin biocides in the EU, can be an explanation for a possible detection of residues in the urine of EU citizens.

The toxicokinetics of cyfluthrin and β-cyfluthrin are similar, and data on cyfluthrin are considered representative for β-cyfluthrin and vice versa. In both, rodents and humans, cyfluthrin is almost completely and rapidly absorbed after ingestion (≥90%). Absorption is also rapid after inhalation. The volume of distribution, as determined in rodent studies, is about 17% of the body volume, indicating that the distribution is primarily in the extracellular fluid compartment (Hays et al., 2009). Hydrolysis of the ester bond and further oxidative metabolism leads to a number of metabolites, and it appears that cleavage of the ester bond results in substantial detoxification. In studies with rats, the main urinary metabolites were identified as cis/trans 3-(2,2-Dichlorovinyl)-2, 2-dimethylcyclopropanoic acid (DCCA) as well as its glucuronide, and as 4 fluoro-3-phenoxybenzoic acid (FPBA) as well as conjugated and free 4′-hydroxy-FPBA. Studies in humans also show the excretion of DCCA and FPBA in urine after cyfluthrin exposure (ATSDR, 2003; Hays et al., 2009; US EPA, 2019a). DCCA is not specific for cyfluthrin and also FPBA is not only known as a metabolite of cyfluthrin, but also as a metabolite of flumethrin, which is used in veterinary medicine. However, human exposure to flumethrin is thought to be very limited and measured urinary FPBA concentrations are likely to reflect recent exposure to cyfluthrin/β-cyfluthrin (Leng et al., 1997a). Quantitative data on the excretion of metabolites is available from a study with controlled oral exposure to cyfluthrin (Leng et al., 1997a). In this study a single male volunteer received a single oral dose of 0.03 mg/kg bw/d (total dose: 2.66 mg). Urine samples were collected at 12-h intervals for 2 days, starting 6 h after exposure. For the quantification of metabolites, the urine samples were acid-treated for the cleavage of conjugates, extracted and subjected to methylation of the free acid metabolites. Separation and detection were performed by GC-MS with a limit of detection of 0.5 μg/L for all metabolites (Leng et al., 1997a). The appearance of metabolites in urine could be described by first-order kinetics with a half-life of elimination of 6.44 h (cis-DCCA: 6.7 h, trans-DCCA: 6.5 h, FPBA: 6.1 h), similar to the results obtained in an inhalation exposure study by Leng et al., 1997b. The authors further found that "in comparison with the intake of 2.6 mg, a total of 1 mg cyfluthrin equivalent was recovered in the urine." Furthermore, of this 1 mg cyfluthrin equivalent, "the total amount of FPBA was twice as much as the total amount of cis/trans-DCCA" (Leng et al., 1997a). This translates into 0.66 mg FPBA excreted in urine following an oral dose of 2.6 mg cyfluthrin, corresponding to a mass fraction of 0.25 (0.66/2.6) FPBA excreted in urine. On a molar basis, this equates to a fraction of 0.47 (Hays et al., 2009). The fraction of FPBA not recovered in urine is likely to be eliminated via faecal excretion or as unmonitored other metabolites in urine (Hays et al., 2009; Leng et al., 1997a).

Epidemiological studies on cyfluthrin did not allow for establishing a relationship between the internal biomarker concentration and critical health effects. In line with the methodology for deriving HBM-GVs, the second option was explored: whether a TRV is available and adequate to derive an HBM-GV. There are 6 evaluations by recognized bodies on cyfluthrin and β-cyfluthrin with derivations of TRVs. Four of them are current, from the years 2018–2020 (EC, 2020/EFSA, 2020 – in the frame of the plant protection products regulation; EC, 2018d – biocidal products regulation; US EPA, 2020; Health Canada, 2018). According to these assessments, the critical effect of cyfluthrin/β-cyfluthrin is neurotoxicity, and quantitatively, beta-cyfluthrin, being the biologically active component of cyfluthrin, is more potent than cyfluthrin. However, biomonitoring via the nearly specific metabolite FPBA no longer allows a distinction to be made here. In studies with several animal species, acute neurotoxic effects were observed at doses lower than those leading to other adverse effects or histological changes in organs. Based on the available findings, there is no evidence of genotoxic or carcinogenic effects of cyfluthrin/β-cyfluthrin. Effects on fertility or development were not or only observed at higher doses, and β-cyfluthrin was concluded unlikely to have endocrine-disrupting properties.

An ADI value of 0.01 mg/kg bw/d was derived from a 4-week rat study with β-cyfluthrin under the EU plant protection products framework (EC, 2017a; EC, 2017b; EC, 2020; EFSA, 2020). This ADI was based on a NOAEL of 1 mg/kg bw/d for acute neurotoxicity, using a standard assessment factor of 100. The rationale for selecting this study as a key study was as follows: The acute toxicity/neurotoxicity of β-cyfluthrin/cyfluthrin is the critical endpoint. This applies also to repeated-dose studies. Due to intensive metabolism and rapid excretion of β-cyfluthrin/cyfluthrin, daily administrations of β-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications. With respect to the occurrence of clinical symptoms, the lowest NOAEL from the repeated-dose study is 1 mg/kg bw/d. Clinical symptoms were evident at the next higher dose of 4 mg/kg bw/d. For cyfluthrin, an ADI of 0.02 mg/kg bw/d was derived under the EU biocidal products regulation based on the NOAEL of 2.0 mg/kg bw/d from an acute neurotoxicity study with rats as well as from a 90 days neurotoxicity study with rats (EC, 2018d). An acute RfD for β-cyfluthrin was derived by the U.S. EPA based on the acute neurotoxicity study in rats by Wolansky et al. (2006) in which 2 h after dosing the decrease in total motor activity was assessed (ED30). EPA performed a benchmark calculation to derive a $BMDL_{1SD}$ of 1.17 mg/kg bw/d. Factors of 10 each for inter- and intraspecies extrapolation were used to derive the acute dietary RfD of 0.0117 mg/kg bw/d for all age groups (US EPA, 2020). The ADI of 0.005 mg/kg bw/d for β-cyfluthrin derived by Health Canada (2017; 2018) is based on a $BMDL_{20}$ of 1.4 mg/kg bw/d for decreased motor activity also from the Wolansky et al. (2006) study. If it is taken into account that Health Canada applies an additional "pesticide factor", which the European bodies do not use, the values in the overall view are very similar despite different approaches and suggest to take the ADI of 0.01 mg/kg bw/d for β-cyfluthrin/cyfluthrin to further derive HBM-GVs.

The ADI as external TRV can be translated into a corresponding $HBM\text{-}GV_{GenPop}$ by using the following mass balance equation, assuming steady-state conditions:

$$HBM\text{-}GV_{GenPop} = \frac{\mathbf{ADI} \bullet \left[\frac{\mathbf{MW(FPBA) \bullet Fue(FPBA)}}{\mathbf{MW(Cyfluthrin)}}\right]}{\mathbf{Daily\ urinary\ flow\ rate\ adjusted\ to\ the\ bw}}$$

Here is MW the molecular weight (FPBA: 232.2 g/mol, cyfluthrin: 434.3 g/mol, ratio: 0.535) and Fue the molar excretion factor 0.47 for FPBA over two days (Leng et al., 1997a). Relating, in a simplified approach, the calculated excretion to the weight proportional amount of urine per day (0.03 L/kg bw/d for children and 0.02 L/kg bw/d for adults (Apel et al., 2020b), the ADI for β-cyfluthrin/cyfluthrin corresponds to the following concentration of FPBA in urine:

Children: 0.01 mg/kg bw/d•0.535•0.47:0.03 L/kg bw/d = 0.0838 mg/L

Adults: 0.01 mg/kg bw/d•0.535•0.47:0.02 L/kg bw/d = 0.1256 mg/L

On this basis, HBM-GV_{GenPop} of 80.0 μg FPBA/L urine for children and 130 μg FPBA/L urine for adults were derived for the interpretation of biomonitoring results on cyfluthin exposure in the general population.

The proportion of cyfluthrin excreted as FPBA in human urine after oral ingestion is subject to great uncertainty, the reported value of 25% expressed as a mass fraction (47% on a molar basis) of an oral dose is based on a single study with a single individual. Other human inhalation exposure studies to cyfluthrin suggest a factor of about three in the interindividual variability of the amount of FPBA excreted in urine. Therefore, the level of confidence related to this aspect is rated as low and additional toxicokinetic studies or the development of appropriate models are recommended to improve the level of confidence in this respect. The overall level of confidence in the HBM-GV is rated as "medium" due to the large database on toxicity.

For information and comparison, the HBM-GVs derived here are lower by a factor of 2–5 compared to the BE values derived by Hays et al. in 2009 (200–400 μg/L total FPBA in urine). This is partly due to the fact that here the ADI for beta-cyfluthrin was used, but also because the health-based exposure guidance values for cyfluthrin from various agencies have been lowered over time. In addition, it should be noted that Hays et al. used slightly different anthropometric and physiological parameters for calculating the BE: average bodyweights from US EPA (2008), average 24-h urine volumes for children from Remer et al. (2006), average 24-h urine volumes for adults from Perucca et al. (2007). Hays et al. (2009) note that the appearance of FPBA in urine has a half-life of about 6 h so that one day corresponds to four half-lives, resulting in approximately 94% of total excretion of FPBA in the first day following an acute exposure. Therefore, a BE for acute exposure will almost be identical to a BE for a chronic RfD or ADI assuming steady-state (100% of a daily dose excreted per day).

The limits of quantification and detection (LoQs/LoDs) of analytical methods applied are at least about two or three orders of magnitude lower than the HBM-GV proposed. For example, a sensitive method was described by Schettgen et al. (2016) for the simultaneous quantification of eight metabolites of synthetic pyrethroids, including FPBA, in urine of the general population. The method comprises acid hydrolysis of the conjugates, followed by a pH-controlled extraction into n-hexane, derivatization with n-tert-butyldimethylsilyl-n-methyltrifluoroacetamid (MTBSTFA) and quantification by GC/MS/MS using deuterium- and 13C-labelled standards. This method has a limit of quantification of 0.01 μg/L. The 5th report on human biomonitoring of environmental chemicals in Canada describes a method using hydrolysis with glucuronidase followed by extraction, derivatization with hexafluoro-2-propanol and diisopropylcarbodiimide and GC/MS detection using 13C-FPBA as an internal standard. For this method, a LoD of 0.006 μg/L is reported (Health Canada, 2019).

3.2.2. Phthalates and DINCH

Phthalates have long been used in the manufacture of flexible PVC and are found in many consumer-related products. Some are considered as substances of very high concern (SVHC) and are meanwhile regulated, so the effectiveness of restrictions as well as the change of use patterns of substitutes should be controlled by HBM. For selected substances of this substance group and DINCH as a substitute, HBM-GVs for the general population were derived (Lange et al., 2021). In 5 out of 6 cases, the basis of derivation was a TRV, specifically for DEHP (TDI), DnBP (DNEL), DiBP (DNEL), DPHP (RfD) and DINCH (TDI). HBM-GVs derived for adults and children, refer with regard to the phthalates DEHP, DnBP, and DiBP to anti-androgenicity, in view of DPHP to effects on the thyroid and in view of DINCH to nephrotoxicity. Table 2 summarizes the essential information on critical impact endpoints, TRVs, toxicokinetic aspects, relevant biomarkers of exposure and numerical values for the HBM-GV_{GenPop} together with their level of confidence. With regard to BBzP, Lange et al. (2021) decided not to use the TDI value of 0.5 mg/kg bw/d (EFSA, 2005b) for deriving HBM-GVs for the general population. This TDI is based on reduced anogenital distance in F1 and F2 males at 250 mg/kg bw/d, however Howdeshell et al. (2008) showed that BBzP has similar potency to suppress foetal testosterone as DEHP, DiBP and DnBP. Therefore, it cannot be ruled out that effects could be observed at lower doses than the 50 mg/kg bw/d dose tested in the key study used by EFSA. Thus, Lange et al. (2021) decided to use other toxicologically relevant values derived from experimental studies with animals (see Table 3).

3.2.3. Bisphenols – bisphenol A (BPA)

Human exposure to bisphenol A (BPA) is widespread and of particular concern because of its known endocrine-disrupting properties. BPA is considered to be more toxicologically active than the conjugated forms (e.g. BPA-glucuronide (BPA-G) and BPA-sulfate (BPA-S)), and its measurement in blood would be a better 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, total BPA in urine (i.e. the sum of free and conjugated forms of BPA measured after hydrolysis of phase II metabolites) was retained as the relevant exposure biomarker for BPA. The derivation of the HBM-GVs for total BPA by Ougier et al. (2021a) was made based on the concentrations of urinary total BPA equivalent to the 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). 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 and the human physiologically-based pharmacokinetic (PBPK) model developed by Karrer et al. (2018), assuming an oral exposure to BPA at the t-TDI level averaged over 24 h (Ougier et al., 2021a).

For workers, 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, 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 as would a 24h-averaged intake according to the European Chemicals Agency's oral DNEL of 8 μg BPA/kg bw/day set for workers (ECHA, 2015). 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 by Ougier et al. (2021a), 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.

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) recently released for consultation a re-evaluation of their t-TDI set in 2015 (EFSA, 2021). According to this proposal, the new TDI would be established at 0.04 ng/kg bw/d of total BPA. This value is 10^5 times lower than the current t-TDI. In fact, when recalculating the HBM-GVs for total BPA in urine of the general population, on the basis of this new TDI proposal, and by the means of the PBPK model by Karrer (2018), the HBM-GV would have to be divided by 10^5 (2.3 ng/L for adults and 1.4 ng/L for children). Thus, the risk for consumers related to BPA exposure would be of concern with regard to this new value proposed, and protective measures would need to be taken (Meslin et al., 2022).

3.2.4. Mycotoxins – deoxynivalenol (DON)

Deoxynivalenol (DON) is a naturally occurring mycotoxin produced mainly by Fusarium graminearum and F. culmorum. The general population is exposed to DON through the consumption of contaminated foodstuff, especially grain-based products. Maximum levels for DON in foodstuffs for human consumption have been established in Regulation (EC) No 1881/2006 (EC, 2006). In the absence of human data to derive an HBM-GV_{GenPop} for DON, and in the absence of new toxicological studies showing chronic effects other than reduction in body weight gain

Table 3
Derivation of HBM-GVs according to option 3, based on a POD.

Substance/ Exposure biomarker/ Biological material	Critical effect	POD [mg/kg bw/d]/key study/Assessment factors (AFs)	Toxicokinetics	HBM-GV_{GenPop} [mg/L]	HBM-GV_{Worker} [mg/L]	Level of confidence (LoC)
DEHP/5-cx-MEPP/urine	Aspermatogenesis and reprotoxicity	NOAEL = 5.8 (David et al., 2000) Total AF: 50	Mass balance approach, 5-cx-MEPP, $Fue_{(48h/24h)}$: 0.139/0.132 (Anderson et al., 2011)		0.62	Medium
DnBP/MnBP/ urine	After *in utero* exposure (GD 12 – GD 19): Reduction of foetal testosterone and reduction in expression of key genes encoding proteins involved in cholesterol transport and steroidogenesis	NOEL = 10 (Lehmann et al., 2004) Total AF: 100	Mass balance approach, $Fue_{(24h)}$: 0.69 Anderson et al. (2001)		3	Medium
DiBP/MiBP/urine	After *in utero* exposure (GD 12 – GD 19): Reduction of foetal testosterone and reduction in expression of key genes encoding proteins involved in cholesterol transport and steroidogenesis	POD = 12.5 Read across with DnBP considering 25% potency difference (Lehmann et al., 2004) Total AF: 100	Mass balance approach, Fue $_{(24h)}$: 0.7 (Koch et al., 2012)		3.5	Low
BBzP/MBzP/ urine	After *in utero* exposure: Suppression of foetal testicular testosterone production; reduced serum testosterone and reduced epididymal sperm count and motility in F1 adult rats	LO(A)ELs: 100 (Furr et al., 2014/Ahmad et al., 2014) Total AF: 900	Mass balance approach, $Fue_{(24h)}$: 0.73 Anderson et al. (2001)	Children: 2 Adults: 3	3	Medium
DPHP/oxo-MPHP & OH-MPHP/ urine DPHP/oxo-MPHP/urine DPHP/OH-MPHP/urine	Follicular hypertrophy of the thyroid gland in F0 rats	Human equivalent $BMD_{10}L_{95}$: 6.1 (BASF, 1995; Bhat et al., 2014) Total AF: 45	Mass balance approach, oxo-MPHP, $Fue_{(24h)}$: 0.0795; OH-MPHP, $Fue_{(24h)}$: 0.0597 (averaged values, Leng et al., 2014 & Klein et al., 2018)		0.7 0.4 0.3	Low
BPS/Total BPS/ urine	Mammary gland and neuro-behavioural toxicity	LOAEL: 0.002 (Kolla et al., 2018, 2019; Catanese and Vandenberg, 2017) Total AF: 75	PBPK model by Karrer et al. (2018), 24h constant (worker discon-tinuous) exposure to 0.0266 μg/kg bw/day	0.001	0.003	Medium-low
NMP/5-HNMP & 2-HMSI/urine	Maternal and developmental toxic effects seen in a study on developmental toxicity	NOAEL: 125 (Saillenfait et al., 2002) Total AF: 300	Mass balance approach, 5-HNMP, $Fue_{(9d)}$: 0.44; 2-HMSI, $Fue_{(9d)}$: 0.20 Åkesson & Jönsson (1997)	Children: 10 Adolescents/ adults: 15		Medium
NEP/5-HNEP & 2-HESI/urine	Foetus weight, variations of the skeleton seen in a study on developmental toxicity	NOAEL: 50 LOAEL: 250 (Saillenfait et al., 2007) Total AF: 100	Mass balance approach, 5-HNEP, $Fue_{(96h)}$: 0.289; 2-HESI, Fue $_{(96h)}$: 0.216 Koch et al. (2014)	Children: 10 Adolescents/ adults: 15		Medium-low
DMAC/tNMAC/ urine	Liver toxicity	NOAEC = 25 ppm (Malley et al., 1995) Total AF: 12.5	Correlation atmospheric DMAC and urinary tNMAC: LnCNMAC (mg/g cr) = 0.894 × lnCDMAC(ppm) + 2.47 R2 = 0.54 (Spies et al., 1995a) Log(CNMAC mg/g cr) = 0.685 + 0.455 log (CDMAC mg/m^3) R2 = 0.497 and $p < 0.001$ (Qian et al., 2012)		12 mg/g creat for total NMAC	Medium-low

HBM-GV_{GenPop} = Human biomonitoring guidance value for the general population; DEHP = diethyl hexyl phthalate; 5-oxo-MEHP = mono(2-ethyl-5-oxohexyl) phthalate; 5-OH-MEHP = mono(2-ethyl-5-hydroxyhexyl) phthalate; 5-cx-MEPP = mono (5-carboxy-2-ethylpentyl) phthalate; DnBP = di-n-butyl phthalate; MnBP = monobutyl phthalate; DiBP = diisobutyl phthalate; MiBP = monoisobutyl phthalate; BBzP = butyl benzyl phthalate; MBzP = monobenzyl phthalate; DPHP = bis-(2-propylheptyl) phthalate; oxo-MPHP = mono(propyl-6-oxo-heptyl) phthalate; OH-MPHP = hydroxy-mono-propylheptyl phthalate; BPS: bisphenol S; NEP: N-methyl-2-pyrrolidone; 5-HNMP: 5-hydroxy-N-methyl-2-pyrrolidone; 2-HMSI: 2-hydroxy-N-methylsuccinimide; NEP: N-Ethyl-2-pyrrolidone; 5-HNEP: 5-hydroxy-N-ethyl-2-pyrrolidone; 2-HESI: 2-hydroxy-N-ethylsuccinimide; DMAC: N,N-dimethylacetamide; tNMAC: total N-methylacetamide; Fue = fractional urinary excretion coefficient or urinary excretion factor; AF = assessment factor; POD = point of departure; bw = body weight; NO(A)EL = no observed (adverse) effect level; LOAEL = lowest observed (adverse) effect level; NOAEC = no observed adverse effect concentration; BMDL = benchmark dose lower confidence limit.

as critical, the group TDI for the sum of DON and its acetylated and modified forms set by EFSA in 2017 (EFSA, 2017) was used by Van den Brand et al. (2021) as a starting point for deriving an HBM-GV_{GenPop}. EFSA's Panel on Contamination in the Food Chain (CONTAM) decided to characterize the hazard for the sum of DON, its acetylated forms (3-Ac-DON, 15-Ac-DON) and DON-3-glucoside together, both for chronic and for acute adverse health effects in humans, assuming that i) 3-Ac-DON, 15-Ac-DON and DON-3-glucoside are all metabolized to DON and absorbed to the same extent as DON, ii) the acetylated forms of DON induce the same acute and chronic adverse health effects as DON and iii) similar acute and chronic adverse health effects of DON-3-glucoside as of DON cannot be excluded. The key study (Iverson et al., 1995) selected by EFSA (2017) is a two-year long-term study on mice. Data for both sexes were combined and a lower 95% confidence limit for a benchmark response of 5% additional risk ($BMDL_{05}$) of 0.11 mg/kg bw/d for reduced body weight gain was calculated by EFSA (2017). A group TDI of 1 μg DON/kg bw/d was then set for the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside by using the default assessment factor of 100 for inter- and intraspecies variability. Since the BMDL values calculated for developmental and reproductive toxicity were all larger than the $BMDL_{05}$ of 0.11 mg DON/kg bw/d, the CONTAM Panel concluded that the group TDI was also protective for developmental and reproductive toxicity (EFSA, 2017).

Regarding toxicokinetic data in humans, there is one comprehensive quantitative study on DON urinary excretion profile and metabolism after oral exposure (Vidal et al., 2018; Mengelers et al., 2019). This intervention study involved 20 adult volunteers, including 11 women (55%) and 9 men (45%) at a mean age of 32 years, range 18–61 years. The volunteers followed a diet free of cereals and cereal products for two days before and two days after the administration date. 16 volunteers were administered a single oral dose of DON at the level of the group TDI (1 μg/kg bw), while 4 volunteers served as controls. The individual urine was collected during 24 h after administration and samples were analysed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). DON was rapidly excreted within 24 h, the total DON recovered (free DON + DON glucuronides) was 64.0 ± 22.8% of the administered DON on a molar basis. DON-15-glucuronide was the most prominent urinary biomarker followed by free DON and DON-3-glucuronide. In a further approach, Mengelers et al. (2019) determined the so-called 'reverse dosimetry factor' (RDF). The RDF is the ratio of the intake of a substance to the calculated cumulative excreted amount and is the inverse of the urinary excretion factor Fue. Because the distribution of the ratios was skewed, a logistic transformation was applied to calculate the confidence bounds. According to this, the RDF for total DON is 1.45 (CI 1.03–7.10) and the Fue for total DON is 0.69 with a confidence interval of 0.14–0.97. The derivation of the HBM-GV by Van den Brand et al. (2021) is based on this urinary excretion factor (Fue) of total DON calculated by Mengelers et al. (2019) at 0.69.

Due to the fact that a single dose of DON in humans is almost completely excreted within 12 h of the last exposure to DON and even in case of three exposure time points per day (breakfast, lunch and evening meal) a steady-state will not be reached because the elimination half-lives of all biomarkers are shorter than the dosing interval, a large variation is expected in the excreted amount of DON in a spot urine sample. Thus, it was decided to relate the HBM-GV for DON in urine to a 24-h urine sample, with an average 24h urinary flow rate of 29.4 mL/kg bw/d, as determined by Mengelers et al. (2019):

$$\mathrm{HBM-GV_{GenPop}} = \frac{\textbf{Group TDI} \bullet \textbf{Fue (total DON in 24h)}}{\textbf{Daily urinary flow rate adjusted to the bw}}$$

On this basis the calculated HBM-GV for the general population is (1 μg/kg bw/d•0.69): 29.4 mL/kg bw/d = 0.023 mg/L or 23 μg/L. A differentiation according to age was not made.

The level of confidence in this value is regarded as "medium". Using the confidence interval around the Fue, the following confidence interval around the HBM-GV for total DON was calculated: 0.005–0.033 μg/mL. Due to the short elimination half-life of total DON (<3h) the HBM-GV for DON (23 μg/L) cannot be used for a spot urine sample because the variation in the total DON concentration in such a sample will be much larger than the confidence interval calculated for a 24h urine sample (Van den Brand et al., 2021).

3.3. Third option: HBM-GVs based on a point of departure from an experimental (animal) study

According to option 3, the derivation of HBM-GVs from experimental (here animal) test results, values for nine substances were derived within the framework of HBM4EU: for the phthalates DEHP, DnBP, DiBP, and DPHP for workers; for the phthalate BBzP as well as for bisphenol S (BPS) for both, the general population and workers; for the solvents N-methyl-2-pyrrolidone and N-ethyl-2-pyrrolidone for the general population, and for the solvent N,N-dimethylacetamide for workers. The information on their derivation and the respective numerical values are summarized in Table 3.

3.3.1. Phthalates

HBM-GVs for selected phthalates to apply to workers have all been derived from PODs of animal studies, in particular for DEHP, DnBP, DiBP, BBzP, and DPHP. In addition, the HBM-GV for BBzP to apply to the general population, was also derived on the basis of two PODs from animal studies (Lange et al., 2021). For DEHP, DnBP, DiBP and DPHP, the critical study chosen for deriving the corresponding occupational HBM-GV differs from that chosen for deriving the HBM-GV_{GenPop}, as such studies were chosen that most closely reflect the exposure scenario at the workplace. That is, experimental designs with exposure of adult animals, including exposure in the first trimester of pregnancy, are considered more transferable to the working population. On the other hand, women should no longer be occupationally exposed to classified reproductive toxins from the time they report their pregnancy to the employer (usually from the second trimester of pregnancy) and during breastfeeding, so that this exposure period is considered rather inappropriate.

HBM-GVs for the phthalates DEHP, DnBP, DiBP and BBzP refer to anti-androgenic effect endpoints, for DPHP to effects on the thyroid. Regarding the HBM-GV_{Worker} for DnBP, DiBP and BBzP, the selected critical endpoints are related to the effects on the offspring after *in utero* exposure. Since in this case no differences in the sensitivity of fetuses carried by women from the general population and fetuses carried by working women can be assumed, a default assessment factor (AF) of 10 was applied to the respective PODs for within-species differences instead of the default value of 5 normally applied for systemic effects on the working population as a more homogeneous population. As the critical endpoint selected for deriving the DEHP HBM-GV_{Worker} is bilateral aspermatogenesis observed in adult rats, an AF of 5 was retained in that case. Table 3 provides an overview of the most important parameters to derive the HBM-GVs as well as the relevant biomarkers of exposure and the numerical values themselves.

3.3.2. Bisphenols – bisphenol S (BPS)

BPS is used for epoxy resins, in coatings for cans, in the production of plastics, especially in polycarbonate plastics, as additive in dyes and tanning agents (Chen et al., 2016), and in thermal paper as a substitute for BPA (ECHA, 2020d; Björnsdotter et al., 2017). Absorption of BPS by humans occurs predominantly orally while dermal absorption of BPS by humans proved to be limited (Khmiri et al., 2020). This section summarizes the derivation of HBM-GVs for BPS previously published by Meslin et al. (2022). According to the authors, available human data on BPS is insufficient for the derivation of HBM-GVs, and no TRVs have yet been published by the EU institutions or other recognized international organizations. However, numerous results from animal experiments with BPS show convincingly adverse effects on female reproduction,

neurodevelopment and mammary gland (Beausoleil et al., 2022). The sensitivity to BPS is clearly dependent on the timing of exposure, with specific periods of development being critical. Disruption of estrogenic signaling is likely central in the mediation of these effects although other modes of action may be involved (Almeida et al., 2019; Le Magueresse-Battistoni et al., 2018; Mhaouty-Kodja et al., 2018). The LOAELs of 2 μg/kg bw/d for mammary gland and neurobehavioral toxicity determined in oral studies with perinatal exposure of mice (Kolla et al., 2018, 2019; Catanese and Vandenberg, 2017) were selected by Meslin et al. (2022) as POD for the derivation of HBM-GVs. Appreciating that the clearance of BPS is mainly driven by its glucuronidation and that major differences exist between BPS and BPA toxicokinetics with a lesser capacity for elimination and a 100-fold higher oral bioavailability of BPS compared to BPA, Meslin et al. (2022) translated the POD into the corresponding human urine level of total BPS by using the PBPK model by Karrer et al. (2018). This was based on a 100% oral exposure scenario for the general population as well as for workers. While continuous exposure was assumed for the general population, the workers exposure was adjusted to occupational conditions (discontinuous, 5 days per week, 8 h per working day followed by a non-exposure period of 16 h). Once the human equivalent dose was derived, different assessment factors were applied to estimate the HBM-GVs. A factor of 3 was applied for extrapolating the LOAEL to the NOAEL, an assessment factor of 2.5 for remaining interspecies differences (mostly for toxicodynamic differences) and a factor of 10 accounting for intra-species differences. Generally, this factor is set to 5 when workers are the targeted population for which the HBM-GV is derived (ECHA, 2012). However, as the most sensitive endpoint(s) to be protected from are the effects on the unborn child, no differences can be assumed between the foetuses of the general population and of the workers. The HBM-GV_{GenPop} was rounded to 1.0 μg/L and should be applied to the whole general population. The HBM-GV_{Worker} was rounded to 3.0 μg/L. The level of confidence attributed to the HBM-GVs for the general and working population was set to 'medium-low' (Meslin et al., 2022).

3.3.3. Solvents

3.3.3.1. Pyrrolidones. N-methyl-2-pyrrolidone (NMP) is an aprotic and medium polar organic solvent which is completely miscible with water. It is used e.g. for extraction purposes in the petrochemical industry, in the production of polymers (membranes), in stripping and cleaning applications in the microelectronics industry, in coating products, in waterborne paints and in functional fluids like coolants, insulators, refrigerants, hydraulic fluids. Different consumer products may include NMP, such as (printer) inks, toners, coatings, cleaners (RIVM, 2013). N-Ethyl-2-pyrrolidone (NEP), also a polar aprotic solvent, is used in many applications as substitute for the structural analogue NMP.

Consumers are expected to be exposed to NEP by using anti-freezing products, coating products, lubricants and greases, adhesives and sealants, air care products, non-metal-surface treatment products, inks and toners, leather treatment products, polishes, waxes and cleaning products (ECHA, 2011b). Exposure to both substances is mainly via the skin and the respiratory tract.

Specific biomarkers of exposure in urine are 5-HNMP (5-hydroxy-N-methyl-2-pyrrolidone) and 2-HMSI (2-hydroxy-N-methylsuccinimide) for NMP and 5-HNEP (5-hydroxy-N-ethyl-2-pyrrolidone) and 2-HESI (2-hydroxy-N-ethylsuccinimide) for NEP (Åkesson and Jönsson, 1997; Koch et al., 2014; RIVM, 2013). Half-lives of the urine metabolites are 4 h for 5-HNMP, 17 h for 2-HMSI, 7 h for 5-HNEP and 27 h for 2-HESI. David et al. derived in 2021 HBM-GV_{GenPop} for the sum of the respective specific metabolites of NMP and NEP.

Based on the knowledge that reproductive toxicity is the most critical effect of NMP (ECHA, 2020b), one key oral developmental study from Saillenfait et al. (2002) on rats and one supporting oral reproductive toxicity study from Sitarek et al. (2012) on rats were selected for the determination of a POD. Although the oral pathway is secondary due to the indications for use of NMP, oral studies were used for the derivation of HBM-GVs, as a conceivable derivation of HBM-GVs based on animal studies with dermal administration was considered too uncertain due to differences in dermal absorption in rodents and humans. With regard to the question of whether it is possible to extrapolate to the inhalation route, it was investigated and confirmed that the NOAEC of the main inhalation study by Saillenfait et al. (2003), which was used by RIVM (2013) to derive the $DNEL_{inhalation}$ for workers (including pregnant women), would result in a body burden of a similar magnitude.

The study of Saillenfait et al. (2002) resulted in a NOAEL of 125 mg/kg bw/d for maternal and developmental toxic effects, that was only slightly below the 150 mg/kg bw/d that showed already maternal and developmental toxic effects in the study of Sitarek et al. (2012). Since no NOAEL could be determined in the Sitarek et al. study (2012), and since the distance between NOAEL and LOAEL of the two studies is small, an additional assessment factor of 3 was applied to the NOAEL of 125 mg/kg bw/d from the Saillenfait et al. (2002) study to consider the uncertainties in the underlying database. In order to account for inter- and intraspecies differences further assessment factors of 10 each were applied resulting in a TRV-like value of 0.42 mg/kg bw/d. Finally, an HBM-GV_{GenPop} of 15 mg/L for adolescents/adults and 10 mg/L for children was determined for the sum of the selected urine exposure biomarkers 5-HNMP und 2-HMSI with excretion fractions of 44% for 5-HNMP (Fue: 0.44) and 20% for 2-HMSI (Fue: 0.20) (Åkesson and Jönsson, 1997).

Also for NEP, reproductive toxicity is the most critical effect endpoint (ECHA, 2020a) and David et al. (2021) derived the HBM-GV_{GenPop} in this case on the basis of a developmental toxicity study in rats as key study with a LOAEL of 250 mg/kg bw/d and a NOAEL of 50 mg/kg bw/d (Saillenfait et al., 2007), supported by a developmental toxicity study in rabbits with a LOAEL of 200 mg/kg bw/d and a NOAEL of 60 mg/kg bw/d (BASF, 2007). Assessment factors for inter- and intraspecies variability of 10 each resulted in a TRV-like value of 0.5 mg/kg bw/d. Finally, an HBM-GV_{GenPop} of 15 mg/L for adolescents/adults and 10 mg/L for children was calculated for the sum of the selected urine exposure biomarkers 5-HNEP and 2-HESI based on excretion fractions of 28.9% for 5-HNEP ($Fue_{(96\ h)}$: 0.289) and 21.6% for 2- HESI ($Fue_{(96\ h)}$: 0.216) (Koch et al., 2014).

The overall level of confidence (LoC) considering uncertainties in e.g. reliability of the key study used to derive the TRV-like value, uncertainties related to the extrapolations leading to the TRV-like value, to toxicokinetic data on the substance of interest, and to the calculation of the final HBM-GV was set by David et al. (2021) to 'medium' for NMP and 'medium-low' for NEP.

3.3.3.2. N,N-dimethylacetamide (DMAC). In the EU, DMAC is predominantly used in the production of agrochemicals, pharmaceuticals and fine chemicals, accounting for 65–70% of tonnage. About 20–25% of EU tonnage is used in the production of man-made fibres which are mainly used for the production of clothing. DMAC is also used as a solvent in coatings for industrial use (approximately 3–5% of EU tonnage). Non-occupational exposure to DMAC is uncommon. At workplace, DMAC exposure occurs by inhalation and dermal routes. The literature provides occupational studies with relationships between exposure and health effects, and between exposure and biomarkers concentrations. There is no data linking biomarker levels and health effects.

Although the metabolite S-acetamidomethyl-mercapturic acid (AMMA) in urine may be a relevant biomarker of DMAC, sufficient data to allow the derivation of a biological value are according to research by Meslin et al. (2021) only available for total N-methylacetamide (tNMAC), which is the sum of N-hydroxymethyl-N-methylacetamide and NMAC.

After it was determined by Meslin et al. (2021) that a derivation of an HBM-GV according to the second option is not possible, because on the

one hand SCOEL recommendations are outdated, on the other hand assessment factors were applied for the derivation of MAK or ACGIH values, which are neither consistent with ECHA nor HBM4EU methodology, they proposed initially as part of the third option a TRV-like value of 2 ppm. This TRV-like value is based on the NOAEC of 25 ppm for the most sensitive effect endpoint "hepatotoxicity" resulting from the study by Malley et al. (1995), and on the application of assessment factors of 2.5 for the extrapolation to humans and 5 to take into account interindividual variabilities in the working world (note: the Malley et al. (1995) study was also key study for MAK and ACGIH values derivation.).

In a further step, the most relevant studies providing correlations between DMAC concentration in air and tNMAC in urine were selected (Spies et al., 1995; Qian et al., 2012), allowing the calculation of an HBM-GV_{Worker} of 12 mg/g creat for total NMAC based on the TRV-like value. The sampling time recommended for comparison of analytical results with this HBM-GV is at the end of the shift after at least two days of exposure.

The derivation of the HBM-GV_{Worker} presents according to Meslin et al. (2021) many uncertainties: lack of data on relationship between health effects and biomarker levels, calculation of a TRV-like value and the use of a correlation between airborne DMAC levels and biomarkers, despite of a potentially significant dermal contribution on intake. The level of confidence to this value is therefore given "medium-low".

4. Discussion - obstacles in derivation and limitations in interpretation of HBM-GVs

The synopsis of the results shows that the approach of deriving HBM-GVs based on a relationship between human internal biomarker concentrations and adverse health effects, which is considered to be the most suitable, could only be applied for few substances within the framework of the HBM4EU activities. In addition to cadmium and DMF, this also applies to mercury, although further consultation is still required, so that these values have been classified as provisional for the time being. Although numerous results from human studies are available for some substances, including phthalates and pyrethroids, several limitations do not allow to use these data. This is due to the following reasons, among others: Although longitudinal studies are most suitable for linking exposures to health outcomes, a cross-sectional design was often chosen by research groups instead of a longitudinal design, and the results of individual samples do not in themselves allow conclusions to be drawn about earlier events leading to the observed health effects. Furthermore, the health questionnaires that accompany human biomonitoring are not always targeted enough to conclude causality. Many of the studies cannot exclude effects from co-exposures and often the long latency period between exposure and effect makes interpretation difficult. The possibility of exposure misclassification was also considered a limitation, as exposure determination was mostly based on a single sample. In some cases, concentrations of exposure biomarkers were below the LoD of the method, which meant that suboptimal statistical evaluations and/or default assumptions had to be made. Also, sometimes the results of the studies were seen as contradictory or inconsistent and did not necessarily lead to a unified conclusion.

TRV values such as TDI, ADI, or OEL from recognized national and international bodies, on the other hand, represent - as long as they are still current and a minimum of TK data and/or correlations between exposure and exposure biomarker levels are available - a valuable basis for a less complex derivation of HBM-GVs. One drawback here is the update of guidance values which is lagging far behind the generation of new toxicological data and knowledge – this process has to speed up. The working group which derived the HBM-GVs under HBM4EU has made use of this approach in nine cases and it seems appropriate to establish a mutual information mechanism for further activities, so that e.g. upcoming amendments to a TDI, such as for BPA, can be directly included in the derivation process and conversely, research results of large EU projects can be used by European bodies in a timely manner (e.g. elaborations on BPS).

Deriving HBM-GVs based on a POD of an animal experiment can sometimes be more difficult because comparatively few studies are available for some substances. For example, chronic studies may be missing, the number of animal species studied may be small, or the exposure pathway may not be the most relevant for humans. Also, the dosing regimen may not be sufficient to derive meaningful dose-effect relationships or to determine a NOAEL. In these cases, extrapolation is necessary so that the level of confidence for values derived under such conditions is in general lower. In this way, according to the third option, HBM-GVs were derived for nine substances, whose level of confidence lies between low and medium.

When deriving HBM-GVs for the biological medium urine using the simple urine mass balance approach, the proportion of the absorbed substance that is excreted in the form of the respective biomarker over a certain time (Fue) plays an essential role. Unfortunately, this Fue is often calculated on the basis of data from a few volunteers which do not fully cover inter-individual variability, e.g. according to age or gender. Also, usually only a few dose levels are examined. This uncertainty in the calculation of an HBM-GV must be taken into account when interpreting the measured data, as must the body weight-dependant urinary flow rate, which is subject to variation within- and between individuals, but is likely to have increased on average over time. So, the German HBM Commission assumes an excretion rate of 20 mL/kg bw/d for adults. Aylward et al. (2015) came, after a literature review, to a similar statement that the urinary flow rates in adults were consistent across the range of ages from 15 to 80, averaging approximately 20 mL/kg bw/d with no consistent differences between males and females, but a high coefficient of variation (in the order of 100% based on spot samples). Lermen et al. (2019) showed then in 2019 that geometric mean values for daily urinary flow rates of young adults (20–30 years) increased from 1997 to 2016 with a similar rate in both sexes (in males by 32%, from 1532 mL/24 h in 1997 to 2039 mL/24 h in 2016; in females by 36% from 1459 mL/24 h in 1997 to 1987 mL/24 h in 2016) meaning 33.12 mL/kg bw/d for females and 25,5 mL/kg bw/d for males which is confirmed by Mengelers et al. (2019) with a 24-h urinary flow rate of 29.4 ± 8.5 mL/kg bw/d determined on 20 volunteers. Thus, a certain degree of uncertainty must be assumed, which becomes particularly relevant when measured concentrations are close to the HBM-GV and thus the margin of safety is low. To reduce this uncertainty in general, further data collection, especially on urinary flow rate for children and pregnant women is recommended. It must also be decided whether the median or rather the 95th percentile should be the appropriate reference parameter.

For some substances, PBPK models are available which can predict the absorption, distribution, metabolism and excretion (ADME) of chemicals in humans or animals. These models facilitate the transfer of findings or assumptions from one species to another or the extrapolation from one exposure pathway to another (e.g. inhalation to oral). For BPA, a model is available with which the oral and dermal uptake, the subsequent distribution in blood, and the excretion in urine can be calculated, so that more precise statements on kinetics and a more precise HBM-GV derivation are possible. In order to improve risk assessments, such models need to be developed all the more urgently for substances whose measured biomarker concentration is close to an HBM-GV calculated with simpler one-compartment models. Thus, a tiered approach is suggested, based on the amount and quality of data available: 1st tier one-compartment modelling based derivation of HBM-GV, 2nd tier in cases e.g. where the risk characterization ratio is close to 1, refinement by PBPK modelling, and 3rd tier, most robust, supplementary determination and use of correlations between external exposure to specific chemicals and the concentration of the chemical itself and/or its metabolite(s) in the human body.

Although HBM - compared to external exposure assessment – provides a better estimate of actual exposure by direct measurement of the chemicals or their metabolites in the human body, thus reducing

uncertainties in health-based risk assessment, uncertainties remain in discontinuous exposure to substances with short biological half-lives of the biomarkers of exposure. This is why for the analysis of individual samples, 24 h urine collections instead of spot urine samples are recommended. However, on a population basis, this aspect is not relevant: spot and 24 h urine samples produce comparable results provided that the population is large enough (Christensen et al., 2012) and sampling is at random in relation to meal ingestion and bladder-emptying times. However, the analysis also suggests that caution should be exercised when interpreting the high end of spot sample data sets. For workers, HBM-GVs are recommended associated with a sampling time, which is mainly based on half-lives.

So far, HBM-GVs have only been derived for single substance risk assessment. But different substances with similar mechanisms of action occur simultaneously in the environment. For the assessment of such real mixtures, the Hazard Index Approach can be applied (Apel et al., 2020a; Lange et al., this issue) or a MAF (mixture assessment factor) can be introduced. Other working groups under HBM4EU have explored this topic in more depth and developed initial proposals (Kortenkamp, 2020; Socianu et al., 2022).

5. Conclusions and future challenges

The derivation and application of health-based guidance values in the context of HBM4EU has shown that HBM-GVs are an effective tool for an easy and comprehensible evaluation of HBM results. Used at the population level, these values can not only help to refine public health risk assessment, but also indicate potential regulatory priorities and the need for (additional) measures to reduce exposure or for continuous monitoring. At the individual level a careful interpretation is necessary recognising the limitations of these values and taking into account individual and environmental factors as well as personal behaviours. It must also be kept in mind that HBM data are not necessarily obtained in the most sensitive exposure window, they only show the internal exposure at a certain point in time, which may not be the critical age or life circumstance (for example pregnancy).

The establishment of a commonly agreed upon procedure for deriving HBM-GVs (Apel et al., 2020b), as well as the consultation of experts from all partner countries prior to finalizing the values, has led to this type of assessment tool becoming better known, more widely used and broadly quality assured. Furthermore, even in other working contexts corresponding values have been derived based on the concept paper (Tarazona et al., 2022). These values have not yet gone through a consultation process and are therefore referred to as "provisional" HBM-GVs. Within the framework of the recently launched project PARC (The European Partnership for the Assessment of Risks from Chemicals) this agreement on content is to be made up for.

Since HBM-GVs describe a threshold concentration at and below which no health effect is to be expected, no HBM-GVs can usually be derived for genotoxic carcinogens. Nevertheless, an analogous calculation method can be used to derive risk-based values for internal exposure from external doses that relate to specific additional lifetime cancer risks. This was done for chromium VI by deriving an HBM Exposure Equivalent for Cancer Risk (HBM-EECR) in the amount of 8 μg/g creatinine for workers of the chrome-plating sector (corresponding to an excess lifetime risk of 20 cases of lung cancer per 1000 workers) (Sissoko et al., 2022).

The work on the derivation of HBM-GVs is to be continued under PARC, whereby PBPK modelling and the evaluation of HBM results on substance mixtures will play a greater role. It is also planned to intensify the mutual transfer of information at international level (i-HBM Working Group; OECD Occupational Biomonitoring, see references) in order to avoid duplication of work and to achieve mutual recognition of interpretation standards.

New scientific findings may require a re-evaluation of substances. HBM-GVs must therefore be checked from time to time with regard to new scientific findings and updated if necessary.

Declarations of interest

None.

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