



Health-related interpretation of human biomonitoring results – new and updated human biomonitoring guidance values from PARC and HBM4EU

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ARTICLE INFO

Keywords:

PARC
HBM4EU
Human biomonitoring guidance values
HBM-GV
HBM-EECR

ABSTRACT

During the first three years of the Partnership for the Assessment of Risks from Chemicals (PARC), we derived health-based human biomonitoring guidance values (HBM-GVs) for 11 substances to enable the direct health-related interpretation of human biomonitoring (HBM) results. HBM-GVs indicate the concentration threshold of the substance or its specific metabolite(s) in human biological samples up to which according to current knowledge no adverse health effects are expected, assuming exposure to the individual substance alone. New HBM-GVs are now available for the pesticides' active ingredients gamma-/lambda-cyhalothrin, acetamiprid, and imidacloprid, the ortho-phthalate diisononyl phthalate (DiNP) and the ortho-phthalate substitute diethylhexyl terephthalate (DEHTP), the UV filters DHHB (diethylamino hydroxybenzoyl hexyl benzoate, Uvinul® A plus) and benzophenone-3, the metals aluminium and its inorganic compounds, methyl mercury and elemental/inorganic mercury, and nickel. In addition, we updated the HBM-GVs, which were derived as part of the European HBM4EU initiative using the mass balance approach, in light of new findings regarding the body mass normalised daily urine volumes and taking into account consistent rounding in the calculation and presentation of the values. For one substance, chromium VI, we updated HBM Exposure Equivalents for Cancer Risk (HBM-EECR) for workers exposed to highly soluble chromates, e.g. in the chrome-plating sector, and newly derived HBM-EECR for workers exposed to chromium (VI) oxides formed under hot conditions, e.g. in welding. In addition, we drew up an HBM-GV-related scoping document for selected per- and polyfluoroalkyl substances (PFAS). The main conclusions of the work described above are summarised in this publication.

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<https://doi.org/10.1016/j.ijheh.2026.114905>

Received 18 June 2026; Received in revised form 8 September 2026; Accepted 8 September 2026

Available online 12 October 2026

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1. Introduction

The Partnership for the Assessment of Risks from Chemicals (PARC) (Marx-Stoelting et al., 2023) was launched as a follow-up project to the HBM4EU initiative (Ganzleben et al., 2017; Kolossa-Gehring et al., 2023a, 2023b) to develop next-generation chemical risk assessment aimed at protecting human health and the environment. It supports hereby the European Union's Chemicals Strategy for Sustainability and the European Green Deal's "Zero Pollution" ambition. Within the PARC framework, we derived health-based human biomonitoring guidance values (HBM-GVs) for 11 substances for the health-related interpretation of human biomonitoring (HBM) results that will emerge from the PARC general population and occupational HBM surveys as well as from further national or international surveys. HBM-GVs can be directly compared with HBM data. They indicate the concentration threshold of the substance or its specific metabolite(s) in human biological samples up to which according to current knowledge no adverse health effects are expected, assuming exposure to the individual substance alone. For one substance, the carcinogenic chromium VI, we derived HBM Exposure Equivalents for Cancer Risk (HBM-EECR) covering exposure to highly soluble chromates and to chromium (VI) oxide fumes. HBM-EECRs are derived for non-threshold carcinogens, for which it is not possible to identify a safe level of exposure. In addition, we conducted a feasibility study for the PFAS compounds included in the PARC general population HBM survey to determine whether deriving HBM-GVs would be justified and whether the available data are sufficient to support this process.

A human biomonitoring guidance value for the general population (HBM-GV_{GenPop}) refers to lifetime exposure to an individual substance. An exceedance of the HBM-GV_{GenPop} may trigger health surveillance of the population concerned, and should be a reason to identify exposure sources and appropriate measures to reduce exposure (Apel et al., 2020). An HBM-GV derived for occupationally exposed adults (HBM-GV_{Worker}) represents the concentration of a substance or its specific metabolite(s) in human biological media aiming to protect workers exposed to the respective substance regularly (each work day), and over the course of a working life from adverse effects.

Our HBM-GVs were developed as part of the PARC project P4.1.3.1.a and subsequently subjected to further expert consultations on a voluntary basis, coordinated by the national hubs of PARC.¹ Therefore, these values provide a good foundation for the uniform and harmonized health-based interpretation of human biomonitoring data obtained within the framework of PARC and beyond. Governmental decision-makers can use the assessment results as a first step to identify potential regulatory and risk management needs or to evaluate the effectiveness of measures that have already been implemented. HBM-GVs play also an important role in communication, e.g. with the public or with experts from different fields, such as health care. In addition, because people are usually exposed to multiple chemicals at the same time (Luijten et al., 2023), HBM-GVs provide a valuable basis for assessing combined exposures (Lange et al., 2022). HBM-GVs can also be set for groups of substances, e.g. PFAS. The methodology used to derive HBM-GVs is also applicable to further approaches to risk assessment of mixtures. For example, the procedure for deriving HBM-GVs is being applied in the PARC Real Life Mixtures project (McKeon et al., 2025), which advances the use of HBM data in evaluating health risks from chemical mixtures.²

¹ The National Hubs are networks of organizations at the country level, involving PARC partners, the relevant national ministries, public and research institutions and other stakeholders (e.g., industry, NGOs, trade unions) active in the field of human biomonitoring, environmental monitoring, toxicology and chemical risk assessment outside the umbrella of PARC.

² <https://www.eu-parc.eu/projects/enhancing-risk-assessment-chemical-mixtures>.

This article summarizes the results of work described above and also includes an update of selected HBM-GVs derived within the framework of HBM4EU for which the calculation basis has changed due to updated physiological parameters for the mass balance approach.

2. Methods

The general methodological approach for deriving HBM-GVs, including a consultation procedure with experts, has been published by Apel et al. in 2020. In principle, there are three options for HBM-GV derivation depending on the availability of data, their quality, and their relevance. The first and preferred option is the derivation of HBM-GVs based on human data that establish causal relationships between internal concentrations and health effects in population-based studies. The second option is the HBM-GV derivation based on a defined external toxicological (toxicity) reference value (TRV) and, the third option is the derivation based on a critical effect observed in experimental (animal) studies (Apel et al., 2020). Physiologically based pharmacokinetic (PBPK) models and mass balance approaches are applied to estimate internal exposure if option 2 or 3 is selected. Criteria for the selection of exposure biomarkers for HBM studies include the characterisation of a relationship between biomarker concentrations and health effects and/or external concentrations or doses, the elimination half-life (to assess the biomarker's suitability for the exposure interval), the specificity of the biomarker, and the availability of sufficiently sensitive analytical methods (ANSES, 2025). Urine is the preferred biological matrix for water-soluble substances and their excretion products, as it provides a good overview of current or short-term exposure, while blood is more suitable for accumulating substances for determining long-term exposure. Regarding the mass balance approach for urinary excretion, the general formula when considering the parent compound is:

$$HBM - GV = TRV \times \frac{Fue(\text{Parent compound})}{\text{Body mass normalised daily urine volume}}$$

If one metabolite has to be taken into account as biomarker, the following formula applies:

$$HBM - GV = TRV \times \frac{\left(\frac{M(\text{Metabolite}) \times Fue(\text{Metabolite})}{M(\text{Substance})} \right)}{\text{Body mass normalised daily urine volume}}$$

If two metabolites are to be taken into account as biomarkers, the following formula applies:

$$HBM - GV = TRV \times \frac{\left(\frac{M(\text{Metabolite 1}) \times Fue(\text{Metabolite 1}) + M(\text{Metabolite 2}) \times Fue(\text{Metabolite 2})}{M(\text{Substance})} \right)}{\text{Body mass normalised daily urine volume}}$$

TRV: toxicological/toxicity reference value (from a recognised scientific institution and also, for ease of reading, analogue values which we have derived ourselves on the basis of a suitable PoD), M: molar mass, Fue: urinary excretion fraction (molar basis).

The body mass normalised daily urine volumes previously used for the derivation of HBM-GVs under HBM4EU were based on recommendations from the German Human Biomonitoring Commission (HBM Commission) (Apel et al., 2020). However, in the further development of its concepts, the HBM Commission presented in 2025 new comprehensive data analyses suggesting a change in the previously used default values for body mass normalised daily urine volumes (uV) of 0.020 L/kg bw/d for adults (HBM Commission, 2025). The analysis of 24-h urine samples from young adults (N = 6846, 20-29 years old) from the German Environmental Specimen Bank from 2010 to 2024 showed a significant increase in daily urine volume in men and especially in women, as well as a significant increase in 24-h urine volume normalised to body mass. Based on the median for the years 2020 to 2024, default values for body mass normalised urine excretion per day of 0.030 L/kg bw/d for men and 0.035 L/kg bw/d for women were

established. No large, up-to-date dataset on 24-h urine volume in children was available. However, the default value of 0.030 L/kg bw/d previously used is supported by data from a cohort of children aged 2–6 years (N = 68, urine collection period 2014/2015) and was therefore retained by the HBM Commission (HBM Commission, 2025; Lermen et al., 2019). This well-documented update of the scientific evidence was incorporated into the derivation of the HBM-GVs within the PARC framework. The HBM-GVs derived under the HBM4EU initiative using the mass balance approach (Lange et al., 2021; David et al., 2021; Apel et al., 2023) were also updated with the new default values.

For a systematic literature search, a search string was developed consisting of (A) a health part³ and (B) synonyms for the substance in question and its major metabolites. The search was carried out in SCOPUS and Pubmed. To derive HBM-GVs, we gave priority to the most recent and scientifically reliable publications; for example, where toxicity studies in animals closely adhered to the Klimisch or ToxRTool criteria (Klimisch et al., 1997; Schneider et al., 2009) or where an analysis of a risk of bias had been carried out for epidemiological data (e. g. using the ROBINS-I tool). In addition, most recent reports on derived limit values from both European and international authorities were taken into consideration. An overview of new and updated HBM-GVs can be found in Table 8.

3. Derivation of HBM-GVs for selected substances

3.1. Pesticides' active ingredients

3.1.1. Pyrethroids – gamma-/lambda-cyhalothrin

The synthetic pyrethroids cyhalothrin⁴ and gamma-cyhalothrin (CAS No. 76703-62-3)⁵ are not authorized in Europe according to Regulation 1107/2009, but the isomer lambda-cyhalothrin (CAS No. 91465-08-6) is approved as an insecticide for plant protection until 31/01/2029.⁶ In addition, exposure to (gamma-/lambda-) cyhalothrin via imported goods, especially food (Morgan, 2020), cannot be ruled out for the general population.

Urine levels of the cyhalothrin metabolite cis-3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropanecarboxylic acid (ClF3CA) reflect recent exposure. ClF3CA is also a metabolite of the synthetic pyrethroids bifenthrin and tefluthrin. However, bifenthrin is no longer approved in pesticides or biocides and tefluthrin is approved in the EU only as a niche product, as an insecticide in capsule suspension for seed coating applied in professional seed treatment facilities. Whilst imported foodstuffs cannot be ruled out as a potential source of exposure to bifenthrin and tefluthrin, this potential contribution to overall exposure is considered to be low. Thus, urinary ClF3CA concentration is largely attributed to exposure to cyhalothrin and its isomers and considered a suitable exposure biomarker for these substances. A sensitive chemical analytical method was described by Schettgen et al. (2016) for the simultaneous quantification of eight metabolites of synthetic pyrethroids, including ClF3CA, in urine obtained from the general population (limit of quantification (LoQ): 0.01 µg/L). This method also includes the detection of the bifenthrin metabolite 2-methyl-3-phenylbenzoic

acid, so that any exposure to bifenthrin via foodstuffs imported into the EU can be detected and a distinction can be made between exposure to these two pyrethroids. If necessary, tefluthrin could also be detected analytically using a combination of metabolite analyses (e.g. including 4-methyl-2,3,5,6-tetrafluorobenzyl alcohol).

Regarding toxicity of cyhalothrin and its isomers, we drew on numerous publications, including EC, 2020/2021; EFSA, 2014a/2014b/2019a/2020a/2021; U.S. EPA, 2020; FAO and WHO, 2019. In the end, we used the European Food Safety Authority's Acceptable Daily Intake (ADI) value for gamma-cyhalothrin of 1.2 µg/kg bw/d (EFSA, 2014a/EC, 2021) as lowest and conservative value for the HBM-GV derivation as it is not possible, within the context of HBM, to distinguish between exposure to different cyhalothrin isomers. The ADI for gamma-cyhalothrin is based on the endpoint “reduced body weight gain” in rat offspring of a multi-generation study. However, it must be noted that the acute reference doses (ARfDs) derived by Health Canada (2021) and U.S. EPA (2020) based on neurotoxic effects are of a similar order of magnitude. Studies on acute neurotoxicity and neurotoxicity following repeated administration of cyhalothrin and its isomers have also shown that repeated exposure does not result in lower PoD values. This observation is consistent with the general kinetic profile for pyrethroids and allows the conclusion that choosing an acute neurotoxic endpoint as PoD for the derivation of HBM-GVs would also be protective in the long-term. Consequently, compliance with the ADI (set by the European Commission) and the HBM-GVs based on this ADI also protects the general population against neurotoxic effects resulting from long-term exposure to cyhalothrin and its isomers.

The urinary excretion fraction (F_{ue}) for ClF3CA used for the mass balance approach is 0.213 (Khemiri et al., 2017; Bouchard et al., 2021), further parameters see Table 1.

ClF3CA in urine, HBM-GV_{GenPop – children/men} = 1.2 µg/kg bw/d x 0.539 x 0.213 ÷ 0.030 L/kg bw/d = 4.6 µg/L

ClF3CA in urine, HBM-GV_{GenPop-women} = 1.2 µg/kg bw/d x 0.539 x 0.213 ÷ 0.035 L/kg bw/d = 3.9 µg/L urine

The fractional urinary excretion of the metabolite ClF3CA showed considerable inter-individual variability (Khemiri et al., 2017; Bouchard et al., 2021); that is why our conservative approach was all the more necessary as a precautionary measure. Our approach, which is based on the lowest ADI value and the updated daily urine volume for adults adjusted for body mass, is the reason why the HBM-GVs for (gamma- and lambda-) cyhalothrin are lower than the values provisionally derived under HBM4EU for lambda cyhalothrin (HBM-GV_{GenPop-children}: 9 µg ClF3CA/L urine; HBM-GV_{GenPop-adults}: 14 µg ClF3CA/L urine) (Tarazona et al., 2022).

3.1.2. Neonicotinoids – acetamiprid

Acetamiprid (CAS No. 135410-20-7) is a chloropyridinyl neonicotinoid insecticide widely used in agriculture (Zhang and Lu, 2022). Furthermore, acetamiprid is approved until 31. January 2027 as an active substance for use in biocidal products of product-type 18 (insecticides, acaricides) (Commission Implementing Regulation (EU) 2018/1129), but only one product, TECHNIVERT, is authorised for limited usage for termite control in France.

Table 1

Summary of parameter values used for the HBM-GV calculation for the gamma-/lambda-cyhalothrin metabolite ClF3CA in urine.

TRV: ADI for gamma-cyhalothrin	1.2 µg/kg bw/d
Molar mass cyhalothrin	449.9 g/mol
Molar mass ClF3CA	242.6 g/mol
Molar mass ratio of ClF3CA to cyhalothrin	0.539
F _{ue} (s _{4h})	0.213
Body mass normalised urine volume per day (uV) _{children and men}	0.030 L/kg bw/d
Body mass normalised urine volume per day (uV) _{women}	0.035 L/kg bw/d

³ (health OR adverse OR toxic* OR neurotox* OR expos* OR epidem* OR cohort OR genotox* OR genetic* OR carc* OR cancer OR reproduct* OR reprotox* OR developmental OR fertil* OR disease OR neurologic* OR metabol* OR ADME OR PBPK OR PBTK OR excret* OR “in vivo” OR “in vitro” OR “in silico” OR endocrine OR “half-life” OR immun* OR MOA OR “mode of action”).

⁴ EU Pesticides Database - Active substances - Active substance details (europa.eu).

⁵ <https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/1211>.

⁶ EU Pesticides Database - Active substances - Active substance details (europa.eu).

N-Desmethyl-acetamiprid (DME-ACE) is considered the biomarker of choice, being a major and specific metabolite of acetamiprid in urine (Wrobel et al., 2023a). Wrobel et al. (2023b) established a specific and robust method to analyse 7 neonicotinoids and neonicotinoid-like compounds (NNIs) together with 9 specific metabolites with an LoQ for acetamiprid of 0.06 µg/L and for DME-ACE of 0.15 µg/L.

An ADI of 25 µg/kg bw/d was proposed by EFSA in 2013 (EFSA PPR Panel, 2013) referring to developmental neurotoxicity. Following our literature review, we still regard the underlying study in rats performed according to U.S. EPA testing guideline OPPTS 870.6300 and in compliance with Good Laboratory Practice (GLP) as key study. The NOAEL of this study is 2.5 mg/kg bw/d and refers to reduced auditory startle response in F1 males. More recently, EFSA published a statement on the toxicological properties and maximum residue levels of acetamiprid and its metabolites where it proposed to reduce both the ADI and acute reference dose (ARfD) values by a factor 5, i.e. from current 25 to 5 µg/kg bw/d due to uncertainties in the evidence for developmental neurotoxicity (EFSA, 2024a). According to Revision 8 of the Renewal Report, the lower values are finalised (SANTE/10502/2017 Rev 8). Also, the new maximum residue levels (MRLs) are already published and entered into force in August 2025, reflecting the lower ADI and ARfD (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L_202500158).

We used the urinary mass balance approach to derive HBM-GVs for DME-ACE. The kinetics study by Wrobel et al. (2023a) was favoured over that of Harada et al. (2016) for determining the Fue because in the latter the external calibration was used without an internal standard. This means that in the Harada et al. (2016) study analyte losses and matrix effects could not be compensated for, and thus, the determination of DME-ACE concentrations is subject to a significantly higher uncertainty than that by Wrobel et al. (2023a). The kinetics study by Wrobel et al. (2023a) resulted in a Fue of 0.54 after 48 h, for further parameters see Table 2.

DME-ACE in urine, HBM-GV_{GenPop – children and men} = 5 µg/kg bw/d x 0.937 x 0.54 ÷ 0.030 L/kg bw/d = 84 µg/L

DME-ACE in urine, HBM-GV_{GenPop – women} = 5 µg/kg bw/d x 0.937 x 0.54 ÷ 0.035 L/kg bw/d = 72 µg/L

The inter-individual differences observed in the Fue of the main metabolite DME-ACE between the volunteers were less than a factor of 2 which falls within the range of biological variation. However, as toxicokinetics could depend on factors such as the test subject's age, sex or ethnicity, there remain uncertainties regarding the extrapolation of the Fue to all population groups. We nevertheless conclude that, whilst there are uncertainties regarding toxicokinetics, the additional assessment factor applied by EFSA to the ADI and its toxicokinetic basis is appropriate for mitigating these uncertainties and results in a precautionary value that is considered appropriate for deriving the HBM-GVs.

The biomonitoring equivalent (BE value) for DME-ACE of 220 µg/L, recently published by Hays et al. (2026), differs from our HBM-GVs because a different ADI (8 µg/kg bw/d, Health Canada (2010)), different body mass normalised daily urine volumes and different excretion fractions were used. Contrary to our assessment, Hays et al. (2026) considered the study results of Harada et al. (2016) and

Wrobel et al. (2023a) to be equivalent and therefore calculated a mean value for the DME-ACE excretion fraction. The Fues were prior to averaging corrected to account for incomplete excretion. We used the Fue value of 0.54 reported by Wrobel et al. (2023a), rather than the Fue value of 0.65 modelled by Hays et al. (2026) for the Wrobel study. Our approach with regard to the Wrobel study is therefore rather conservative; overall, taking both toxicokinetic studies into account, Hays et al. (2026) arrive at a Fue of 0.52 that is only slightly different to the one we have used.

3.1.3. Neonicotinoids – imidacloprid

Imidacloprid (IMI) (CAS No. 138261-41-3) is a neonicotinoid insecticide that was launched on the global market in 1991 (Zhang and Lu, 2022). It is designed to be effective by contact or ingestion and acts on several types of post-synaptic nicotinic acetylcholine receptors (nAChRs) in the nervous system of insects (EFSA PPR Panel, 2013). Since 2018, EU regulations have banned all outdoor uses of imidacloprid in agriculture, restricting its application exclusively to permanently enclosed greenhouses where the exposure of pollinators and other wildlife is minimised (Regulation (EU) 2018/783). IMI is also included in Annex I to Directive 98/8/EC of the European Parliament and of the Council as an active substance for use in biocidal products of product-type 18.

The metabolites 4-/5-OH-IMI and IMI olefin are specific biomarkers of IMI. However, since the analytical method by Wrobel et al. (2023a) does not separate the two isomers 4-/5-OH-IMI, and the detector response for these analytes might differ to some extent, IMI-olefin in urine is regarded as most suitable biomarker for HBM (Wrobel et al., 2023a). Following optimisation of their method, Wrobel et al. (2025) reached an LoQ of 0.24 µg/L for IMI-olefin, so that a sensitive HBM method for this biomarker is available. We therefore used only the 48-h excretion fraction for IMI-olefin - amounting to 27 % - when deriving the HBM-GVs.

The most critical effects of imidacloprid were observed in a combined chronic toxicity/carcinogenicity study in rats according to OECD test guideline 453 and in compliance with GLP. The effects concerned specifically non-neoplastic lesions (decreased body weight gain, changes in clinical chemistry parameters related to hepatotoxicity, and a dose dependent thyroid mineralization) (Eiben, 1991; Eiben and Kaliner, 1991). Related to the thyroid effects, an ADI of 0.06 mg/kg bw/d was derived by EFSA (2013). Furthermore, the current ADI for imidacloprid is considered by EFSA (2013) to be sufficient to protect against possible developmental neurotoxic effects. The literature search and analysis we carried out in PARC did not produce any results that would call this ADI into question, as many of the newer studies exhibit methodological limitations, or fail to demonstrate lower PoDs than the NOAEL used for the ADI derivation. Thus, the ADI served us as the TRV and we used the urinary mass balance approach with the specific metabolite IMI-olefin to derive HBM-GVs for the general population (see also Table 3).

IMI-olefin in urine, HBM-GV_{GenPop – children/men} = 0.06 mg/kg bw/d x 0.99 x 0.27 ÷ 0.030 L/kg bw/d = 0.53 mg/L

IMI-olefin in urine, HBM-GV_{GenPop – women} = 0.06 mg/kg bw/d x 0.99 x 0.27 ÷ 0.035 L/kg bw/d = 0.46 mg/L

Table 2

Summary of parameter values used for the HBM-GV calculation for the acetamiprid metabolite DME-ACE in urine.

TRV: ADI for acetamiprid	5 µg/kg bw/d
Molar mass acetamiprid	222.7 g/mol
Molar mass DME-ACE	208.7 g/mol
Molar mass ratio of DME-ACE to acetamiprid	0.937
Fue _(48h)	0.54
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

Table 3

Summary of parameter values used for the HBM-GV calculation for the imidacloprid metabolite IMI-olefin in urine.

TRV: ADI	0.06 mg/kg bw/d
Molar mass _{IMI}	255.7 g/mol
Molar mass _{IMI-olefin}	253.7 g/mol
Molar mass ratio IMI-olefin to imidacloprid	0.99
Fue _(48h)	0.27
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

The data used to determine the urinary excretion fraction was derived from a study with only three male volunteers, who received a single oral imidacloprid dose of 5 mg (Wrobel et al., 2023a). However, a small sample size is common in kinetic studies in humans conducted for HBM purposes, and this study also showed that the F_{ue} for IMI-Olefin were highly consistent across subjects, with inter-individual variations of a factor of 1.8. As toxicokinetics depend on age, gender or ethnicity of the test subjects, we examined the question of whether the F_{ue} values can nevertheless be applied to all population groups. We conclude that the assessment factor for toxicokinetic variability within humans, which was already applied by EFSA when deriving the ADI, is suitable for mitigating uncertainties, and that the data set is therefore considered suitable for deriving HBM-GVs for the general population.

3.2. Ortho-phthalates and their substitutes

3.2.1. Diisononyl phthalate (DINP)

Diisononyl phthalate (DINP) is not a single compound, but a complex mixture of isomers. Therefore, two different CAS registry numbers were assigned to DINP, 28553-12-0 (DINP-2) and 68515-48-0 (DINP-1). DINP with CAS registry number 28553-12-0 contains more than 50 % of the alcohol component consisting of alkyl-substituted octanols, heptanols or hexanols. DINP with CAS registry number 68515-48-0 is produced by the so-called polygas technology and contains approximately equal amounts of 3,4-; 4,6-; 3,6-; 3,5-; 4,5- and 5,6-dimethylheptan-1-ol. However, both mixtures of isomers share common constituents and cannot be differentiated through their physicochemical properties. DINP is an ortho-phthalate ester used primarily as a plasticizer. The estimated tonnage band for DINP is given as 10⁵ - 10⁶ tons per year aggregated over all REACH registrants (<https://chem.echa.europa.eu/100.044.602/dossier-list/reach/dossiers/active?searchText=DINP>).

The toxicological data and effect profiles show essentially no differences between the two isomer mixtures and they are therefore treated equally from a toxicological and regulatory perspective (BAuA, 2001; Environment Canada and Health Canada, 2015). From an exposure biomonitoring point of view, it is common practice to integrate over all structural isomers of metabolites with the same functional group (OH-MINP, oxo-MINP and carboxy-MINP). Koch et al. (2007) provided evidence of the appropriateness of this approach. They first identified 4-methyloctan-1-ol as one of the major constituents of the alkyl side chains of DINP-1 and DINP-2 and then synthesized the oxidised metabolites based on this specific side chain (7oxo-MMeOP, 7OH-MMeOP, 7carboxy-MMeHP). A comparison of the ion chromatogram of a processed 50 g/L standard in water and a processed urine sample clearly showed the metabolite standards based on the 4-methyloctyl-isomer to be highly representative for all other possible DINP metabolites eluting with the major DINP metabolite peaks found in the native urine samples. According to Koch et al. (2007) the MS/MS fragmentation characteristics seem not to depend on the branching position but on the type of the oxidative modification of the alkyl chain. The carboxy metabolite favours the intact alkyl chain fragment, the hydroxy and oxo modified metabolites favour benzene containing fragments. Therefore, Koch et al. (2007) concluded that the OH-MINP isomers, the oxo-MINP isomers and the carboxy (cx)-MINP isomers each exhibit the same mass fragments, which can be used for quantification.

There are two relevant toxicokinetic studies in humans available. The first human study (Koch and Angerer, 2007) involves a single male volunteer who received a single oral dose of 1.27 mg/kg bw of deuterium-labelled DINP. In contrast, Anderson et al. (2011) conducted a study in ten male and ten female volunteers exposing them to a single oral dose of 0.012 mg/kg bw and 0.121 mg/kg bw of deuterated DINP (D4-DINP) in two separate study periods. More than 90 % of the metabolites were excreted in urine in the first 24 h of collection, the remainder in the second 24 h. Fractional urine excretion of primary and secondary specific metabolites was 3.1 %, 6.6 %, 12.3 % and 10.9 % for the respective MINP, oxo-MINP, OH-MINP and cx-MINP isomers. Since

the data from Anderson et al. (2011) was collected from a relatively large group of volunteers of both sexes, whereas the study by Koch and Angerer (2007) examined only a single volunteer, we consider the data from Anderson et al. (2011) to be more robust and have therefore used them to derive the HBM-GVs. Campbell et al. (2020) developed a DINP PBPK model, for which they also drew on data from the two controlled studies on human exposure. When applied to the single subject urine data reported by Koch and Angerer (2007), the model lies within a factor of two of the data, and the test subject appears to fall within the range specified by Anderson et al. (2011) (Campbell et al., 2020). This supports our preference for the Anderson et al. (2011) study and the excretion fractions presented therein.

Epidemiological studies on DINP published between the beginning of 2018 and the end of 2023 were evaluated by U.S. EPA (2025a). None of these studies could be used for quantitative dose-response assessments, mainly because the study designs were not suitable or because mixtures of substances were present and there was no isolated exposure to DINP. Rather, the studies were considered as providing qualitative support within the weight of scientific evidence. In 2005, EFSA derived a tolerable daily intake (TDI) of 0.15 mg/kg bw/d for DINP, which the same authority confirmed in 2019 (EFSA, 2005 and 2019b). This TDI is based on a publicly available chronic toxicity study in rats by Exxon Biomedical Sciences (1986) showing a NOAEL of 15 mg/kg bw/d with regard to non-peroxisomal proliferation-related chronic hepatic and renal effects. An assessment factor of 100 was applied to derive the TDI of 0.15 mg/kg bw/d. U.S. EPA's most recent risk assessment from January 2025 (U.S. EPA, 2025b) supports the aforementioned TDI and its underlying PoD. The Agency used the animal data from the studies by Exxon Biomedical Sciences (1986) and Lington et al. (1997) and based its derivation of a margin of exposure (MoE) also on the NOAEL of 15 mg/kg bw/d as PoD. The U.S. EPA justifies the choice of the key study and PoD on the grounds that the selected study received a high overall study quality score and is GLP-compliant. Furthermore, the NOAEL represents the most sensitive PoD identified by the U.S. EPA across the 12 relevant studies subjected to dose-response analysis, including four 2-year chronic dietary studies (3 in rats, 1 in mice), six subchronic (13-week) feeding studies (4 in rats, and 1 each in mice and beagles), a one-generation study on reproduction of rats, and a two-generation study on reproduction of rats. With regard to the adverse effects, U.S. EPA stated that at the LOAEL a spectrum of dose-related effects consistent with liver toxicity was observed in male and female rats. The endpoints indicative of liver toxicity on which the PoD is based were from U.S. EPA's perspective robust in that they were observed across species and durations. The U.S. EPA stated further that the non-cancer chronic PoD based on non-cancer liver effects will adequately account for all chronic toxicity - including carcinogenicity - which could potentially result from exposure to DINP (U.S. EPA, 2025c). The U.S. EPA also carried out benchmark dose (BMD) modelling which led to a wide variability of Benchmark Dose Lower Confidence Limits (BMDLs). This and the uncertainty in several modelled results suggested using the NOAEL instead of a BMDL to establish the PoD.

According to a weight of evidence assessment conducted with support of ExxonMobil Biomedical Sciences Inc. (Lea et al., 2025) in accordance with the ECHA/EFSA Endocrine Disruptor Guidance (2018), DINP does not meet the ECHA/EFSA criteria for classification as an endocrine disruptor. DINP did not elicit thyroid-related apical outcomes in vivo and there were no studies available evaluating thyroid hormone levels in vivo. Also, based on the lack of apical outcomes, the authors of the study assume that DINP does not disrupt the estrogen (E)-pathway. For the androgen (A)- and steroidogenesis (S)-pathways, there was only limited evidence to support adverse apical outcomes and no biologically plausible link could be established between the key events in the hypothesized adverse outcome pathway.

We concluded to use the EFSA TDI for the HBM-GV derivation, as recent research and U.S. EPA's risk assessment does not justify the selection of a different PoD. EFSA (2005 and 2019b) also noted that while

liver effects are the most sensitive endpoints for DINP, it also causes a temporary reduction in testosterone levels in fetuses with a no observed effect level (NOEL) of 50 mg/kg bw/d, which means that these effects are covered by the numerical value of the TDI chosen.

HBM-GVs for the sum of the DINP specific single isomer standards representing the sum of all OH-MINP/cx-MiNP isomers (referred to collectively as OH-MINP and cx-MiNP) were derived according to the mass balance approach, parameters see Table 4. Koch et al. (2007) stated that OH-MINP and oxo-MINP are probably the best parameters to monitor short-term DINP exposures while cx-MiNP is the best parameter to monitor longer term or chronic DINP exposures. Taking into consideration a chronic exposure of the general population to DINP together with the longer half-life of the metabolite cx-MiNP, the choice of cx-MiNP as the sole biomarker of exposure for DINP could be justified; Anderson et al. (2011) showed for their study that the relative standard deviation on the mean of the fractional excretion values (mole basis) for cx-MiNP was 28 %. However, as Anderson et al. (2011) also demonstrated that, to some extent at the individual level, a high excretion fraction for one metabolite is counterbalanced by a low excretion fraction for another, we consider the HBM-GV derivation for the sum of the metabolites cx-MiNP and OH-MINP to be appropriate. It should be emphasized at this point that, in this specific case of DINP, the prerequisite for the application of the HBM-GVs in HBM assessment is that in HBM the same mass spectrometric ion transition as in the relevant toxicokinetic study deriving the urinary excretion fractions needs to be analysed, preferably under comparable chromatographic conditions.

The PBPK model by Campbell et al. (2020) mentioned above did not provide any additional benefit on this point, as the model was parameterised using data from the same study by Anderson et al. (2011) that we had used for the mass balance approach. An independent volunteer study would be required to evaluate the model's predictivity.

Sum of OH-MINP and cx-MiNP in urine, HBM-GV_{GenPop - children/men} =
 $0.15 \text{ mg/kg bw/d} \times (0.737 \times 0.123 + 0.770 \times 0.109) \div$
 $0.030 \text{ L/kg bw/d} = 0.87 \text{ mg/L}$

Sum of OH-MINP and cx-MiNP in urine, HBM-GV_{GenPop - women} =
 $0.15 \text{ mg/kg bw/d} \times (0.737 \times 0.123 + 0.770 \times 0.109) \div$
 $0.035 \text{ L/kg bw/d} = 0.75 \text{ mg/L}$

The HBM-GVs determined here differ from the health-related values derived by Hays et al. (2011) and Lange et al. (2022) for the evaluation of HBM results. Hays et al. (2011) derived biomonitoring equivalents for all specific metabolites of DINP, drawing, amongst other things, on the TDI used here, but employed for the calculation the excretion fractions from Koch and Angerer (2007) as well as other body mass normalised 24-h urine volumes. Lange et al. (2022) focused on the mixture toxicity of selected phthalates and, for this purpose, derived provisional HBM-GV_{GenPop} (separately for children and adults) relating to male reproductive health, based on the BMDL₀₅ value of 5.9 mg/kg bw/d established by Kortenkamp and Koch (2020). The toxicokinetic data used are based on the study by Anderson et al. (2011); the body mass normalised 24-h urine volumes are those used at the time by the German HBM Commission. The provisional values derived for mixture toxicity

assessment were labelled "pHBM-GV_{GenPop-MRA}" by Lange et al. (2022).

It should also be noted that, given that the DINP-1 variant, unlike DINP-2, contains between 15 and 25 per cent isodecanol, a degree of uncertainty could be assumed in the derivation and application of the HBM-GVs. Depending on the exposure situation (occupational mono-exposure to a known type of DINP versus consumer exposures from various sources of exposure and different types of DINP), co-exposures to C8 and C10 phthalates should also be considered in exposure and risk assessments for DINP.

3.2.2. Di(2-ethylhexyl) terephthalate (DEHTP)

Di(2-ethylhexyl) terephthalate (DEHTP) (CAS No. 6422-86-2) serves as a substitute for phthalates and is predominantly used in PVC and other polymeric materials, with a presence of up to 30 % in certain products. It can be assumed that DEHTP is mainly ingested orally, as it is used in consumer-related products such as food contact materials, toys, and medical devices, leading mainly to uptake by ingestion. With more frequent use of DEHTP, increasing exposures among the general population have been shown (Lessmann et al., 2019).

Metabolism and urine excretion kinetics of DEHTP were studied in three male volunteers after a single oral dose of 50 mg DEHTP (Lessmann et al., 2016). The predominant specific metabolite excreted in urine until 48 h after the start of exposure was 1-mono-(2-ethyl-5-carboxyl-pentyl) benzene-1,4-dicarboxylate (5cx-MEPTP), which accounted for approximately 13.0 % of the administered dose, followed by 1-mono-(2-ethyl-5-hydroxy-hexyl) benzene-1,4-dicarboxylate (5OH-MEHTP) (mean: 1.8 %) and 1-mono-(2-ethyl-5-oxo-hexyl) benzene-1,4-dicarboxylate (5oxo-MEHTP) (mean: 1.0 %). A further metabolite 1-mono-(2-carboxyl-methyl-hexyl) benzene-1,4-dicarboxylate (2cx-MMHTP) contributed negligibly. A human PBPK model developed on the basis of an existing model to di (2-propylheptyl) phthalate (DPHP) with minor adaptations and model parameterisation based upon in silico, in vitro and human biomonitoring data (McNally et al., 2023) was not further taken into consideration for the derivation of HBM-GVs. Indeed, the model was parameterised based on data from the three male volunteers in the controlled study by Lessmann et al. (2016). An independent volunteer study would be required to assess the model's predictivity.

Having reviewed recent studies on the toxicity of DEHTP and their findings (e.g. Lee et al., 2020; Cho et al., 2021; Long et al., 2021; Pacyga et al., 2021, 2023), we conclude that these are insufficient to call previous assessments into question. Therefore, in line with EFSA (2008a), we consider retinal effects observed in mid and highly dosed Fischer 344 rats relevant for HBM-GV derivation. These findings were derived from a GLP compliant 104 weeks chronic toxicity/carcinogenicity study according to U.S. EPA guideline OPPTS 870.4200. A NOAEL of 1500 ppm was established, corresponding to 79 and 102 mg/kg bw/d for males and females, respectively (Deyo, 2008). Additionally, results of a Benchmark Dose (BMD) modelling of the data are available (Ball et al., 2012). We chose the benchmark dose lower confidence limit 10 (BMDL₁₀) of 54 mg/kg bw/d as PoD and, using a standard overall assessment factor of 100, established an external dose for HBM-GV derivation of 0.54 mg/kg bw/d. We then calculated the HBM-GVs for the specific metabolite 5cx-MEPTP in urine using the mass balance approach and the parameters listed in Table 5. Due to inter-individual differences in the excretion of specific metabolites, we also considered it appropriate to calculate the HBM-GVs for the sum of both metabolites (see also Table 8).

5cx-MEPTP in urine, HBM-GV_{GenPop - children/men} = $0.54 \text{ mg/kg bw/d} \times$
 $0.789 \times 0.13 \div 0.030 \text{ L/kg bw/d} = 1.8 \text{ mg/L}$

5cx-MEPTP in urine, HBM-GV_{GenPop - women} = $0.54 \text{ mg/kg bw/d} \times$
 $0.789 \times 0.13 \div 0.035 \text{ L/kg bw/d} = 1.6 \text{ mg/L}$

Sum of 5cx-MEPTP and 5OH-MEHTP in urine, HBM-GV_{GenPop - children/men} = $0.54 \text{ mg/kg bw/d} \times (0.789 \times 0.13 + 0.754 \times 0.018) \div$
 $0.030 \text{ L/kg bw/d} = 2.1 \text{ mg/L}$

Table 4

Summary of parameter values used for the HBM-GV calculation for the sum of DINP metabolites OH-MINP and cx-MiNP in urine.

TRV: TDI	0.15 mg/kg bw/d
Molar mass _{DINP}	418.6 g/mol
Molar mass _{OH-MINP}	308.4 g/mol
Molar mass _{cx-MiNP}	322.4 g/mol
Molar mass ratio _{OH-MINP/DINP}	0.737
Molar mass ratio _{cx-MiNP/DINP}	0.770
F _{ue(48h, OH-MINP)}	0.123
F _{ue(48h, cx-MiNP)}	0.109
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

Table 5

Summary of parameter values used for the HBM-GV calculations for the DEHTP metabolite 5cx-MEPTP and the sum of DEHTP metabolites 5cx-MEPTP and 5OH-MEHTP in urine.

PoD: BMDL ₁₀	54 mg/kg bw/d
Overall assessment factor	100
External dose for HBM-GV derivation	0.54 mg/kg bw/d
Molar mass _{DEHTP}	390.6 g/mol
Molar mass _{5cx-MEPTP}	308.3 g/mol
Molar mass _{5OH-MEHTP}	294.3 g/mol
Molar mass ratio _{5cx-MEPTP/DEHTP}	0.789
Molar mass ratio _{5OH-MEHTP/DEHTP}	0.754
F _{ue(48h, 5cx-MEPTP)}	0.13
F _{ue(48h, 5OH-MEHTP)}	0.018
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

Sum of 5cx-MEPTP and 5OH-MEHTP in urine, HBM-GV_{GenPop – women} = 0.54 mg/kg bw/d x (0.789 x 0.13 + 0.754 x 0.018) ÷ 0.035 L/kg bw/d = 1.8 mg/L

The derivation of the HBM-GVs is in line with the derivation of HBM-I values by the German HBM Commission (Apel et al., 2017), which also used the BMDL₁₀ of 54 mg/kg bw/d of the Deyo (2008) study as basis and applied assessment factors of 10 each to account for intraspecies and interspecies variability for determining the external dose for the HBM-I value derivation. The current body mass normalised urine volume was recently used to update the values (Kommission Human-Biomonitoring | Umweltbundesamt).

3.3. UV filter

3.3.1. Diethylamino hydroxybenzoyl hexyl benzoate (DHBB)

The UV filter diethylamino hydroxybenzoyl hexyl benzoate (DHBB) (CAS No. 302776-68-7; trade name: Uvinul® A Plus) has a high production volume with ≥ 1000 tons of DHBB manufactured and/or imported per year in the European Economic Area (ECHA registration dossier, 2020). Specific metabolites of this substance were found with noticeable increasing detection rates in human biomonitoring samples from the German Environmental Specimen Bank after 2012 (Scherer et al., 2025).

The analytical method, metabolism and urinary excretion kinetics in humans of DHBB have been published by Stoeckelhuber et al. (2019, 2020). After oral and dermal administration, DHBB itself is not excreted in human urine, but two specific metabolites were identified, 2-(4-ethylamino-2-hydroxybenzoyl)benzoic acid (ethylamino-hydroxybenzoyl-benzoic acid - EHB) and 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid (diethylamino-hydroxybenzoyl-benzoic acid - DHB). The metabolite 2-(4-amino-2-hydroxybenzoyl) benzoic acid (amino-hydroxy benzoyl-benzoic acid - AHB) is suggested to originate also from other sources of exposure, making it less reliable for assessing DHBB exposure (Scherer et al., 2025). In the kinetic study involving five volunteers (men and women), approximately 54 % of the dose was excreted as AHB, EHB and DHB 72 h after oral administration of DHBB, whereas excretion of this metabolites following dermal application of DHBB amounted – for the formulation used - to only up to 0.02 % after 72 h. Stoeckelhuber et al. (2020) back-calculated the DHBB intake for participants from a biomonitoring study based on the excretion rates of the specific metabolites observed following oral administration, as, in addition to absorption through the skin following the application of sunscreen and other cosmetics, absorption is also likely to occur through ingestion via hand-to-mouth contact and through the application of lipstick. Additionally, the absorption of substances from cosmetic products is dependent on several factors, such as the formulation of e.g. the sunscreen, skin anatomy (depending on sex, age, region of the skin, etc.), layer thickness of the cosmetic product, concentration in the cosmetic

product, residence time on the skin, physical activity (resulting in sweating and elevated perfusion of the skin), and so on. Therefore, using metabolite recoveries from a dermal experiment for dose extrapolation to dermal exposures based on biomarker concentrations is subject to a high degree of uncertainty. Oral toxicokinetic data often is more rugged. Unless significant differences in metabolism between dermal and oral uptake occur (this can be investigated with reasonable effort, as described on the example of the UV filter homosalate by Ebert et al. (2024)), in many cases oral toxicokinetic data will be more precise for assessing exposures based on biomonitoring data (e.g., by calculation of oral-dose-equivalent daily intakes). We followed this line of reasoning and used the excretion rates published by Stoeckelhuber et al. (2020) in our calculation of the HBM-GVs.

The database for DHBB is not sufficient to derive an HBM-GV based on the relationship between human internal concentration of exposure biomarker(s) and related health effects. Furthermore, no suitable TRV proposed by a European or relevant non-European institution was found. There is also insufficient evidence to suggest that DHBB affects the endocrine system (Mikkelsen et al., 2015). We considered a two-generation reproduction toxicity study in rats (oral, feed) according to OECD TG 416 as most relevant. The lowest NOAEL determined in this study is 100 mg/kg bw/d due to general parental toxicity and developmental toxicity. This NOAEL served as PoD for the calculation of HBM-GVs, for further information see Table 6.

EHB in urine, HBM-GV_{GenPop – children/men} = 1 mg/kg bw/d x 0.72 x 0.328 ÷ 0.030 L/kg bw/d = 7.9 mg/L

EHB in urine, HBM-GV_{GenPop – women} = 1 mg/kg bw/d x 0.72 x 0.328 ÷ 0.035 L/kg bw/d = 6.7 mg/L

DHB in urine, HBM-GV_{GenPop – children/men} = 1 mg/kg bw/d x 0.79 x 0.051 ÷ 0.030 L/kg bw/d = 1.3 mg/L

DHB in urine, HBM-GV_{GenPop – women} = 1 mg/kg bw/d x 0.79 x 0.051 ÷ 0.035 L/kg bw/d = 1.2 mg/L

For the sum of both metabolites, the resulting HBM-GVs for children and men are 9.2 mg/L, for women 7.9 mg/L.

3.3.2. Benzophenone-3 (BP-3)

Benzophenone-3 (BP-3) (CAS No. 131-57-7), also named 2-hydroxy-4-methoxybenzophenone (HMB), or oxybenzone, is a UV filter widely applied in personal care products (Mustieles et al., 2023). It is also used as UV stabiliser in paints, coatings, and textiles (DEPA, 2015; Li and Kannan, 2018; Xue et al., 2017). BP-3 is manufactured and/or imported into the European Economic Area in quantities of 1000–10,000 tons per year (<https://chem.echa.europa.eu/100.004.575/dossier-list/reach/dossiers/active>). The most important route of exposure to BP-3 in everyday life is likely to be dermal (Mustieles et al., 2023).

A provisional HBM-GV for BP-3 has already been derived under HBM4EU (Woutersen et al., 2022; Rousselle et al., 2022). However, this value has not been the subject of an expert consultation process

Table 6

Summary of parameter values used for the derivation of HBM-GVs for the DHBB metabolites EHB and DHB in urine.

PoD: NOAEL	100 mg/kg bw/d
Overall assessment factor	100
External dose for HBM-GV derivation	1 mg/kg bw/d
Molar mass DHBB	397.5 g/mol
Molar mass EHB	285.3 g/mol
Molar mass DHB	313.3 g/mol
Molar mass ratio EHB/DHBB	285.3/397.5 = 0.72
Molar mass ratio DHB/DHBB	313.3/397.5 = 0.79
F _{ue(72h, EHB)}	0.328
F _{ue(72h, DHB)}	0.051
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

coordinated by the HBM4EU national hubs (Apel et al., 2020) and has therefore not been agreed upon collectively within HBM4EU. For this reason, we reviewed and updated the derivation of the provisional value. In our updated evaluation, reproductive toxicity remained the most sensitive and critical effect for BP-3.

Exposure to BP-3 can be reliably determined by measuring the total (free plus conjugated) concentration of BP-3 in urine (Calafat et al., 2008). An on-line SPE-LC-MS/MS method has been developed for simultaneous biomonitoring of nine UV filters in urine including BP-3 (LoD: 0.3 ng/mL) (Frederiksen et al., 2017). Two human laboratory-based exposure studies (Hayden et al., 1997; Sarveiya et al., 2004) with quantitative data on excretion of BP-3 in urine are available. Hayden et al. (1997) report a BP-3 excretion in urine of 1–2 % of the initial dose, 10 h after initial dermal application in nine healthy adult volunteers. Sarveiya et al. (2004) report that up to 1 % of the initial dose of BP-3 applied to the skin was measured in urine within 48 h. Woutersen et al. (2022) and Rousselle et al. (2022) decided to use a F_{ue} of 0.01 (1 %) as the more conservative value.

The current state of epidemiological knowledge regarding human exposure to BP-3 and whether and how this might affect human health is insufficient to derive HBM-GVs directly from human data. Furthermore, no TRV proposed by recognised institutions (e.g. ADI, RfD) suitable for the derivation of HBM-GVs was found. Thus, our derivation of HBM-GVs relies on findings from toxicity studies in animals and additionally from human toxicokinetic studies. As there are no reliable studies on toxicity following dermal absorption that would be suitable for setting a PoD, we took the PoD from an oral study in rats and assumed, in analogy to the SCCS methodology to derive a Margin of Safety, a good absorption (according to Mutlu et al. (2020) > 95 %). Critical effects that we consider relevant for the derivation of HBM-GVs are in particular reproduction-related effects, but also the reduction in body weight (gain), observed in studies on reproductive and developmental toxicity. We followed SCCS (2020a) and regard the oral study by Nakamura et al. (2015) as the key study. In this reproductive and developmental toxicity study in female rats a NOAEL of 67.9 mg/kg bw/d was derived based on a reduction in the number of spermatocytes per seminiferous tubule in offspring (postnatal day - PND 23) at doses of 207.2 mg/kg bw/d and higher (Nakamura et al., 2015). We then extrapolated the animal PoD to a human equivalent external dose of 0.679 mg/kg bw/d with the application of a standard overall assessment factor of 100 to account for inter- and intraspecies variabilities, in line with ECHA guidance chapter R.8 (ECHA, 2012). For the derivation of the HBM-GVs, we applied the urinary mass balance approach and used parameters as defined in Table 7.

Total BP-3 in urine, HBM-GV_{GenPop – children/men} = 0.679 mg/kg bw/d x 0.01 ÷ 0.030 L/kg bw/d = 0.23 mg/L

Total BP-3 in urine, HBM-GV_{GenPop – women} = 0.679 mg/kg bw/d x 0.01 ÷ 0.035 L/kg bw/d = 0.19 mg/L

Since no suitable toxicokinetic study following oral administration in humans is available, we used the F_{ue} value for the HBM-GV calculation, which was derived from the studies by Hayden et al. (1997) and Sarveiya et al. (2004) following dermal application of BP-3 in humans. This is justified on the basis of comparative studies in rats and mice by Mutlu et al. (2020), which showed that ¹⁴C-labelled BP-3 was very well

absorbed following both oral (gavage) and dermal administration in various dose vehicles (rats, oral: > 95 % after 72 h; rats, dermal: 64–80 % 72 h after dermal administration of 10 mg/kg - with a single exception of only moderate (46 %) absorption for the dermal application of 10 mg BP-3/kg in a lotion).

Asimakopoulos et al. (2014) incorporated a F_{ue} of 0.02, based on Hayden et al. (1997), in the transformation of internal estimates to external intake estimates. The F_{ue} of 0.01 used by us is considered to be the more conservative and overall protective value.

Woutersen et al. (2022) used the same PoD and F_{ue} but incorporated the HBM4EU default average daily creatinine excretion - based on the calculation in Aylward et al. (2009) - in the derivation of the creatinine corrected provisional HBM-GV. With these defaults a provisional HBM-GV of 0.34 mg/g creatinine was derived. We do not endorse this value, as it no longer adds up mathematically when using the updated parameters (daily urine volumes, normalised to body mass). In this context, it would generally be desirable to further analyse the data published by Lermen et al. (2019) on trends in the characteristics of 24-h urine samples, including urinary creatinine, specific gravity, and conductivity. The German HBM Commission's analysis of the data on urine volumes has already led to changes in the default values (HBM Commission, 2025).

3.4. Metals

3.4.1. Aluminium and its inorganic compounds

Aluminium (CAS No. 7429-90-5) is a ubiquitous metal; the diet is the main source of exposure for the general population, as it occurs naturally in the environment, leaches from food contact materials and is used in food additives. Aluminium may also be used in the treatment of drinking water, and aluminium compounds may be present in consumer goods and vaccines. Furthermore, aluminium metal and -compounds have many industrial applications (ATSDR, 2008; JECFA, 2012).

The bioavailability of aluminium is dependent on the nature and speciation of the aluminium substance (ATSDR, 2008). In alveoli, aluminium bioavailability increases with the solubility of the inhaled substances. Studies in workers suggest a mean absorption rate of 1.5–3 % of inhaled aluminium (Yokel and McNamara, 2001; ATSDR, 2008; SCCS, 2020b). Based on daily aluminium dietary consumption and urinary daily excretion, the oral global bioavailability of aluminium from the diet has been estimated to be 0.1–0.3 % (Yokel and McNamara, 2001; ATSDR, 2008; EFSA, 2008b). Once in the body, the aluminium ion binds to blood proteins and is distributed to all tissues, half of aluminium body-burden is in bones and one-fourth in the lung. Aluminium does not undergo metabolism but can be transformed from one species to another. It is primarily eliminated in the urine (95 %) via glomerular filtration (ATSDR, 2008). Urinary aluminium is considered to be the most relevant biomarker of aluminium exposure, as it is relatively sensitive to small changes in external exposure (Riihimäki and Aitio, 2012), and a good association was found between this biomarker and health effects in humans (ANSES, 2024).

Animal studies following exposure to aluminium compounds have reported neurotoxic effects as well as respiratory toxicity, haematological toxicity, adverse effects on the skeleton and, reproductive and developmental toxicity (including neurodevelopmental effects). In humans, some epidemiological studies in workers have reported respiratory adverse effects, however, these studies include confounders, like co-exposure to other toxic chemicals (e.g., crystalline silica, hydrogen fluoride and other fluorides, ozone and ultra-fine particles, etc.). Most population-based studies report on the association between aluminium concentration in drinking water and the risk of Alzheimer's disease and/or dementia, but suffer from multiple methodological limitations. EFSA (2008b) and the World Health Organization (WHO) (JECFA, 2012) have concluded that exposure to aluminium through the food, including drinking water, does not constitute a risk for developing Alzheimer's disease. Furthermore, some epidemiological studies addressed the

Table 7

Summary of parameter values used for the derivation of HBM-GVs for total BP-3 in urine.

PoD: NOAEL	67.9 mg/kg bw/d
Overall assessment factor	100
External dose for HBM-GV derivation	0.679 mg/kg bw/d
F _{ue} (total BP-3)	0.01
uV _{children and men}	0.030 L/kg bw/d
uV _{women}	0.035 L/kg bw/d

association between aluminium exposure and autism spectrum disease but these studies cannot be used for causality assessment (ANSES, 2024, 2025). On the other hand, several epidemiological occupational studies, 21 cross-sectional and 4 longitudinal studies, have assessed internal aluminium load and cognitive impairment (ANSES, 2024, 2025). This effect has been observed in numerous studies involving workers, which is why we have identified it as critical. The longitudinal study we selected as key study was conducted by Buchta et al. (2003) and Kiesswetter et al. (2009) and included over 90 aluminium welders in the car-body construction industry and 50 controls. The study was conducted over 4 years during which a battery of three performance tests was carried out, separated by 2 years, in 1999, 2001 (Buchta et al., 2003) and 2003 (Kiesswetter et al., 2009). At the first examination, included subjects had at least 2 years of Al-welding time. Subjects with neurological diseases not due to the exposure, cerebrovascular diseases, diabetes, head injuries, insufficient knowledge of the German language were excluded. Aluminium concentrations were measured in personal air, as well as in plasma and in urine, in pre-shift and post-shift samples, by graphite furnace atomic absorption spectrometry (GFAAS). Neurobehavioral assessments used a standardized interview, the Standard Progressive Matrices test (SPM), a verbal intelligence test (WST), the European neurobehavioral evaluation system (EURO-NES), a simple reaction time test, the block design test, the trail making test, and four psychomotor performance tests. There was no significant difference of total dust load when welding aluminium between the three examinations ($p = 0.35$), the same applies for the pre- and post-shift internal Al-loads in exposed welders across examinations. No difference in cognitive performances at a urinary level of 37.87 µg/g creatinine (post-shift, after several shifts with exposure) was reported. No significant differences were observed in psychomotor performance and other neurobehavioral tasks between welders and non-welders. Aluminium welders were slightly slower than controls in their cognitive function (based on reaction time) but performed better in tests measuring motor function; this was the only abnormal result in all three examinations and did not increase with exposure duration. A LOAEL of 97 µg/g creatinine (post-shift, after several shifts) from a 4-year longitudinal study of train and truck construction workers (44 workers and 37 controls) was identified based on cognitive impairment testing in exposed workers as compared to non-exposed workers (Buchta et al., 2005; Kiesswetter et al., 2007). Based on these human data in workers, we adopted the NOAEL of 37.87 µg/g creatinine as PoD and rounded to 40 µg/g creatinine for deriving both of the HBM-GVs. For workers, we did not apply an assessment factor to this PoD, but for the general population, we applied an inter-individual assessment factor of 2 as the key study was conducted in a population of workers. This resulted in an HBM-GV_{Worker} of 40 µg/g creatinine and an HBM-GV_{GenPop} of 20 µg/g creatinine. Sampling time is not critical for the general population chronically exposed to aluminium, but to avoid contamination and ensure good reproducibility, it is advisable to take samples in the morning, upon waking or after showering. The studies used to identify the NOAEL reported the results of post-shift and morning samplings after several working days, adjusted to creatinine, which were not different at these two sampling times. Thus, morning urine sampling is not expected to impact the aluminium urinary concentration adjusted to creatinine (Kiesswetter et al., 2009). For workers, samples taken at the end of a shift, after several shifts, are recommended.

It should be noted that, for the general population, the biomonitoring equivalent concentrations (BEs) based on the oral TRV established by JECFA (2012) of 2 mg/kg bw/week (NOAEL of 30 mg/kg bw/week) using the mass balance approach, which yielded a BE of 117 µg/L, or using the 3-compartment kinetic model of Poddalgoda et al. (2021), which yielded a BE of 107.6 µg/L, were much higher than the derived more conservative HBM-GV (20 µg/g creatinine) and were therefore not retained. For the calculation of these BEs, a urinary daily volume of 0.02 L/kg bw per day was considered for a 70 kg bw adult.

Furthermore, for workers, the German MAK Commission (Klotz et al., 2019) established a biological tolerance value (BAT) of 50 µg

Al/g creatinine as a measure in post-shift urine after several shifts. This value was based on the same studies we used as key studies supplemented by an analysis of effect sizes of 12 epidemiological studies on neurocognitive effects in workers exposed to aluminium. This approach allowed to demonstrate that a higher effect size was observed in studies with a median urinary concentration higher than 50 µg/g creatinine in exposed workers, while those studies where the median urine aluminium concentration in the exposed group was below 50 µg/g creatinine had effect sizes considered small by the MAK Commission. In 2025, the MAK Commission considered that there are no recent data that would call this BAT value into question and confirmed the value of 50 µg Al/g creatinine (Michaelson et al., 2025). In our assessment, we did not carry out an analysis of effect sizes because some of the studies considered in this analysis present debatable results.

3.4.2. Nickel

For nickel (CAS No. 7440-02-0), we derived an HBM-GV_{Worker} for soluble nickel based on the RAC (2018) recommendation for an occupational exposure limit (OEL) value of 0.03 mg/m³ for the inhalable fraction of nickel. This value is based on nasal carcinogenicity of nickel compounds. Nickel compounds have been classified as genotoxic carcinogens with a mode-of-action based threshold (ECHA, 2018). For the derivation of the HBM-GV_{Worker}, existing data from occupational studies showing correlations between workplace air nickel levels and worker's urinary nickel levels were used (Tola et al., 1979; Nieboer et al., 1999; Kiilunen et al., 1997a, 1997b; Oliveira et al., 2000; Bernacki et al., 1980; Werner et al., 1999; Ghezzi et al., 1989; Angerer et al. 2010; Rahkonen et al., 1983; Raithel et al., 1987; Emmerling et al., 1989; Sunderman et al., 1986; Stridsklev et al., 2004, 2007; Stanislawska et al., 2020; Angerer, 1995). As all the older equations were based on total dust, we converted total dust to inhalable dust (ECHA, 2018). The most conservative estimate for soluble nickel is given by the equation by Nieboer et al. (1999) resulting in U-Ni levels of approximately 12.5 µg Ni/L at the OEL, which we rounded down to 12 µg Ni/L representing the HBM-GV_{Worker}. No HBM-GV_{Worker} for sparingly soluble nickel is recommended because of the limited bioavailability and urinary excretion. For the general population we regard the TDI value of 13 µg/kg bw/d recommended by EFSA (2020b) as TRV (critical effect: reproductive toxicity). However, due to numerous uncertainties (including fasting versus non-fasting states (Nielsen et al., 1999; Sunderman et al., 1989), the bioavailability of the various nickel species in food, sex-specific differences, and the modelling approach), we were unable to propose a precise HBM-GV_{GenPop} (Weisell-Laitinen et al., in preparation).

3.4.3. Mercury

3.4.3.1. Methylmercury. Methylmercury (MeHg) (CAS No. 22967-92-6) is known for developmental neurotoxicity. Bacteria in the aquatic environment produce MeHg from inorganic mercury (Hg) forms. MeHg bioaccumulates in the food chain, especially in large predatory fish.

The majority of MeHg in the blood and hair arises from fish and seafood consumption, and total Hg in whole blood or hair also reflects dietary MeHg intake. The concentration of MeHg is the largest fraction of total Hg in blood, constituting on average around 80 % (Sogame and Tsukagoshi, 2020) and is also the largest fraction of hair total Hg, constituting approximately 90 % (Berglund et al., 2005).

Previous studies by the HBM4EU project provided a provisional HBM-GV of 3.5 µg Hg/L for blood (Apel et al., 2022). This was based on the EFSA tolerable weekly intake (TWI) of 1.3 µg Hg/kg bw/w, which was rooted in neurodevelopmental concerns (EFSA, 2012). In PARC, we re-assessed and critically analysed data from a literature review previously carried out by HBM4EU covering the period from January 2012 and June 2021 and subsequently complemented it by new findings on cardiovascular health, that EFSA identified as potentially important endpoint in 2012. The reference point used by EFSA to derive a tolerable

weekly intake (TWI) for MeHg of 1.3 µg Hg/kg bw/week was the level of 11.5 mg/kg Hg in maternal hair, based on results from birth cohort studies in the Faroe Island and the Seychelles (EFSA, 2012). To assess whether a revision of the EFSA TWI for MeHg from 2012 was necessary, the HBM4EU initiative evaluated the evidence base available from January 2012 to June 2021 on prenatal MeHg exposure and neurocognitive development in children. The overall outcome of the review of the 43 included studies was that new studies on neurodevelopmental effects published after the risk assessment of MeHg by EFSA in 2012 did not provide sufficient justification for derivation of a new TWI (Halldorsson et al., 2022). This conclusion is supported by a systematic review by Dack et al. (2022) including studies up to December 2020 with measured prenatal Hg exposure and neurodevelopmental functioning using continuous scales in children aged 0–5 years. The final review included 32 papers (15 of high quality), in which neurodevelopmental functioning had been measured by the use of 23 different scales. Mean concentrations of Hg in maternal blood ranged from 0.64 to 3.71 µg Hg/L and mean maternal hair Hg ranged from 0.3 to 5.7 mg/kg. A data synthesis by a meta-analysis was not possible because of the large heterogeneity of study designs and the results were synthesized narratively in six broad domains of neurodevelopmental outcomes. The paper concluded that “based on current evidence, dietary Hg exposure during pregnancy is unlikely to be a risk factor for low neurodevelopmental functioning in early childhood”.

EFSA (2012) stated that it had become evident that the beneficial effects of fish consumption have to be taken into account when studying cardiovascular disease outcomes in relation to MeHg exposure. After all, the autonomic nervous system is a major regulator of the cardiovascular system including heart rate and blood pressure. Therefore, it is suggested that the neurotoxicity of MeHg may be related to cardiovascular effects. We re-assessed the evidence in original papers on cardiovascular disease in relation to Hg exposure, obtained by a literature search in HBM4EU. The conclusion of this re-assessment is that the evidence for association with heart rate variability or blood pressure is not sufficient to support derivation of an HBM-GV and therefore we did not consider it further. The evidence from other developmental endpoints than neurodevelopmental could also not be used to support the derivation of an HBM-GV.

When deriving HBM-GVs for MeHg, we concluded that the reference point originally derived by EFSA in 2012 for neurodevelopmental effects (11.5 mg/kg maternal hair) is still the most suitable. We considered a standard assessment factor of 3.2 ($10^{0.5}$) necessary to account for toxicokinetic differences in the population. No further assessment factor for toxicodynamic differences was needed, since it was considered that total Hg was measured in maternal hair and neurodevelopmental effects were assessed in children, being the most vulnerable population group. This led to an HBM-GV for MeHg in hair of 3.6 mg Hg/kg hair for the general population. Based on the reference point of 11.5 mg/kg maternal hair and using a maternal hair:blood ratio of 250, this reference point in hair corresponds to 46 µg Hg/L blood. We considered that there was a need for an additional assessment factor of 2 to cover the uncertainty in the hair:blood ratio. This is in line with EFSA 2012. Of note, EFSA (2012, there Appendix E, Table E1) reviewed the reported hair:blood ratio and stated that there is a high inter-study and inter-individual variation in this ratio which is still sufficiently covered by a factor of 2. The provisional HBM-GV for MeHg of 3.5 µg Hg/L blood, that was previously derived by HBM4EU (Apel et al., 2022), included an additional assessment factor of 2 for uncertainty in hair measurement. However, this extra factor was not considered necessary anymore. Our group considered furthermore that a standard assessment factor of $10^{0.5}$ for toxicokinetic differences is needed. This leads to an HBM-GV_{GenPop} of 7.2 µg Hg/L ($46 \mu\text{g/L} \div (2 \times 10^{0.5})$), rounded down to 7 µg Hg/L blood. The HBM-GVs for MeHg in hair and blood are expressed as total Hg, since the analyses are most often not speciated.

3.4.3.2. Elemental/inorganic mercury. During the HBM4EU project, a provisional HBM-GV for inorganic mercury for the general population was proposed. At that time, no HBM-GV was derived for elemental mercury (CAS No. 7439-97-6). Within PARC, we updated the HBM-GV for the general population to cover both inorganic and elemental mercury, and we derived an HBM-GV for workers' exposure to inorganic and elemental mercury. Our evaluation builds on the HBM4EU report (Apel et al., 2022), ATSDR (2024), DFG (2012, 2016), German HBM Commission (1999), SCOEL (2007), EFSA (2012), and the opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2015). In addition, we identified and evaluated neurodevelopmental studies published since 2015.

Workers are mainly exposed to mercury vapor via inhalation (ATSDR, 2024). The general population is currently more prominently exposed to mercury vapor through dental amalgams than to inorganic mercury through diet (ATSDR, 2024; Richardson et al., 2011). However, this is likely to change gradually due to the substitution of amalgam with other dental filling materials. Thus, it is expected that inorganic mercury will become a more important exposure source than mercury vapor especially among the younger population. A relatively specific biomarker for elemental and inorganic mercury is total mercury in urine since methylmercury is resorbed in proximal tubule, and therefore limitedly excreted into urine (ATSDR, 2024). However, total mercury in urine cannot specify the difference between elemental mercury and inorganic mercury.

We based the derivation of HBM-GVs for the general population and for workers on occupational studies on elemental mercury. The Wastesson et al. (2006, 2008) study evaluated neurotoxic effects by detecting tremors in chloralkali exposed male workers compared to sex-matched unexposed reference persons. A median cumulative exposure index of 161 years × µg/g creatinine (range 8–1440 years × µg/g creatinine) was calculated. Median exposure time was 13 years. At this level no significantly increased incidence of tremor was observed in chloralkali exposed workers when compared to reference persons. Thus, the Wastesson et al. (2006, 2008) study showed a no adverse effect level for median cumulative urinary exposure of 12.4 µg Hg/g creatinine/year. This result was supported by several other occupational studies indicating effects above this NOAEL (Bast-Pettersen et al., 2005; Ellingsen et al., 2001; Fawer et al., 1983; Langworth et al., 1992a; Frumkin et al., 2001; Mathiesen et al., 1999; Ehrenberg et al., 1991; Cavalleri et al., 1995; Roels et al., 1982, 1985; Piikivi et al., 1984; Meyer-Baron et al., 2002). In addition, kidney toxicity has been detected in the range of 16–50 µg Hg/g creatinine (Alinovi et al., 2002; Barregård et al., 1988; Buchet et al., 1980; Camerino et al., 2002; Cárdenas et al., 1993; Ellingsen et al., 2000; Langworth et al., 1992b; Roels et al., 1982). We therefore chose the value of 12.4 µg Hg/g creatinine/year as POD and neurotoxicity as the most sensitive endpoint.

For the derivation of an HBM-GV_{Worker} we did not consider necessary additional assessment factors as several independent occupational studies covering hundreds of workers report consistent findings, and the inter-individual variability among the worker population was considered sufficiently covered by the data. Based on these considerations, we set an HBM-GV of rounded 12 µg Hg/g creatinine (corresponding to 17 µg Hg/L) in urine for occupational exposure. Conversion from µg/g creatinine to µg/L was calculated according to Santonen et al. (2023) with the equation $\mu\text{g/L} = \mu\text{g/g creatinine} \times \text{mean urine creatinine concentration in g/L}$ using 1.36 g creatinine/L urine as mean creatinine concentration (Cocker et al., 2011). The HBM-GV_{Worker} is also considered to be protective from kidney toxicity.

In order to protect vulnerable population groups, we considered it appropriate to apply an additional assessment factor of 2, resulting in a value of 6 µg Hg/g creatinine in urine (corresponding to 7.5 µg Hg/L) for the general population. Earlier, within the HBM4EU project a provisional HBM-GV_{GenPop} of 7 µg Hg/L was derived for inorganic mercury. This provisional HBM-GV was based on the TWI value set by EFSA. The critical effect was kidney toxicity observed in animals after oral

exposure to inorganic mercury. It also considered other endpoints including developmental toxicity observed in animals at higher doses. It is noted that this provisional HBM-GV is in accordance with the value currently derived for elemental mercury on the basis of human data. Since urinary mercury concentrations do not differentiate between elemental mercury and inorganic mercury, the HBM-GV_{GenPop} needs to be set in a level that protects from both elemental and inorganic mercury. The provisional HBM-GV of 7 µg Hg/L previously derived within the HBM4EU project for inorganic mercury is considered sufficiently protective, also regarding effects observed in mercury vapor exposed humans. Therefore, an HBM-GV_{GenPop} of 7 µg Hg/L (6 µg Hg/g creatinine) is proposed as the HBM-GV_{GenPop} for both elemental and inorganic mercury. This value corresponds to the HBM-I level set already 1999 for mercury in urine by the German HBM Commission (Apel et al., 2017).

3.4.4. Hexavalent chromium [Cr(VI)]

Hexavalent chromium [Cr(VI)] (CAS No.: 18540-29-9) compounds are occupational carcinogens, and the critical effect used to derive assessment values is carcinogenicity (den Braver-Sewradj et al., 2021; SCOEL, 2017; IARC, 2012). Therefore, instead of an HBM-GV derivation, an analogous procedure was applied to derive HBM-EECRs (exposure equivalents for cancer risk). Workplace exposure to carcinogens should be reduced to the lowest level that is technically feasible. However, for OEL setting, a limit must be selected. Up until recently, there has not been a consensus in the EU on occupational cancer risk levels that can be considered acceptable.

Detailed description and justification for the derivation of the HBM-EECR values for Cr(VI) will be given in Mahiout et al. (in preparation). In summary, their derivation in PARC was based on previous work conducted in HBM4EU, where an HBM-EECR was derived for workers in the chrome-plating sector (Sissoko et al., available in Apel et al., 2022). This HBM-EECR corresponds with the European 8-h binding occupational exposure limit value (BOELV) of 5 µg Cr(VI)/m³ (Directive, 2017/2398), equivalent to a predicted excess lifetime lung cancer risk of 20:1000 (SCOEL, 2017), and thus exceeding the desired minimum protection level of 4:1000 applied in several EU Member States and associated countries.

Since then, the European Commission's Advisory Committee on Safety and Health at Work (ACSH) issued an opinion on limit value setting for non-threshold carcinogens using a risk-based approach (ACSH, 2022). In its opinion, the ACSH established that in the future, limit values for non-threshold carcinogens should be set in between the "upper risk level" of 4:1000 predicted cancer cases and the "lower risk level" of 4:100 000 (terminology as defined by the ACSH).

In PARC, we derived an HBM-EECR for a lung cancer risk level of 4:1000, which corresponds to an atmospheric concentration of 1 µg Cr(VI)/m³ (SCOEL, 2017). Because toxicokinetics and carcinogenic potency differ by substance properties, two values were established: (i) 2 µg Cr/g creatinine (≈2.7 µg Cr/L) in urine for exposure to highly soluble Cr(VI) compounds, and (ii) 1 µg Cr/g creatinine (≈1.4 µg Cr/L) for exposure to sparingly soluble Cr(VI) oxides generated in high-temperature processes such as in welding.

3.5. PFAS scoping document

Perfluoroalkyl substances (PFAS) are synthetic fluorinated compounds that are highly persistent in the environment. They spread over a wide range and some are bioaccumulating in both humans and wildlife. In HBM4EU, three different human health risk assessment approaches were used to determine whether European teenagers are at risk of developing adverse health effects resulting from exposure to PFAS: the Hazard Index (HI) approach, the sum value approach as used by EFSA, and the Relative Potency Factor (RPF) approach. All three approaches indicated that the combined exposure to PFAS compounds included in the assessment was too high and could result in a human health risk for a considerable proportion of individuals in the HBM4EU teenager study

population (Bil et al., 2023).

With the ultimate aim for recommendations to derive HBM-GVs for PFAS compounds in the scope of the PARC general survey, we summarised available health-based reference values and international assessments for PFAS compounds, both for non-cancer and for cancer endpoints. In addition, we reviewed and summarised 43 systematic literature reviews of which 25 were meta-analyses, published until November 2024. Also, we reviewed animal and human data presented in a recent literature study of several PFAS compounds published by the German Environment Agency (UBA, 2023). Based on this literature review, further work is needed especially for substances that have a relevant contribution to PFAS exposure such as observed in the HBM4EU Aligned Studies, and where new epidemiological data for the critical effect domains, namely immune system, fertility and reproductive outcomes, cardio-metabolic outcomes, and fetal growth and birth outcomes, became available in recent years (i.e. after the comprehensive assessment of PFAS by EFSA, 2020c). This further work may focus primarily on the EFSA-4 PFAS (PFOA, PFOS, PFNA, PFHxS) with a view to analyse whether the EFSA sum values are still appropriate, including the evaluation of new evidence for causality for increased cholesterol associated with exposures to perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Derivation of HBM-GVs for the full scope of PFAS compounds measured in the PARC general survey may not be justified due to a minor or negligible contribution to internal exposure for some of them, as per current knowledge from HBM4EU. Furthermore, it is proposed to review published cancer data in more detail including several epidemiological studies and the recently published IARC monograph (IARC: International Agency for Research on Cancer) on PFOA and PFOS (classifying PFOA in group 1 and PFOS in group 2B for carcinogenicity; IARC, 2025), as well as cancer risk assessments published in recent years (U.S. EPA, 2024; CAIEPA, 2024; Steenland et al., 2022). This will enable an assessment of whether or not guidance values or cancer slope factors for PFOA and PFOS carcinogenicity are warranted and feasible, considering their dominant contribution to PFAS body burden. Finally, we will also consider to include additional substances (i.e., short chain PFAS) analysed in the PARC targeted HBM studies in children and studies in pregnant women, breastmilk and newborns (<https://www.eu-parc.eu/projects>).

4. Overall discussion and outlook

4.1. Evaluation of 24-h urine samples compared with spot samples

It could be argued that due to the short half-life of excretion of some metabolites more reliable evaluations of the extent of exposure could be made based on 24-h urine collections rather than spot samples. Moreover, a publication by Casas et al. (2018) quantifying the variability of biomarker measurements of many non-persistent chemicals during several time windows shows that for many of these compounds a few dozen samples are required to accurately assess exposure over periods encompassing several months. Therefore, exposure misclassification in epidemiological studies relying on a single collection point is expected to be high. On the other hand, on a population basis, spot and 24-h samples produce rather comparable results, e.g. see: Christensen et al. (2012) "Overall, spot urinary concentrations of DEHP metabolites and BPA have variability roughly comparable with corresponding 24-h average concentrations obtained from a comparable population, suggesting that spot samples can be used to characterise population distributions of intakes. However, the analysis also suggests that caution should be exercised when interpreting the high end of spot sample data sets."

Aylward et al. (2017) examined data sets for analytes with relatively short elimination half-lives from a total of 16 individuals with collection and measurement of serial urine voids over multiple days and showed, that spot sample concentrations at the 95th percentile were similar to or slightly higher than the 95th percentile of the distribution of all 24-h composite void concentrations, and tended to overestimate the

Table 8

HBM-GVs derived under PARC until May 2025 including updated values from HBM4EU, taking into account updated, body mass normalised 24-h urine volumes and systematic rounding of the calculated values.

Parent substance	Biomarker/Human biological material	Critical effect	HBM-GV _{women}	HBM-GV _{men and children} ^a	HBM-GV _{workers} ^b
Pesticides					
Cyfluthrin	FPBA/urine	Acute neurotoxicity	72 µg/L (update)	84 µg/L (update)	
Deltamethrin ^c	DBCA/urine	Lowered body weight, behavioral changes, clinical signs of neurotoxicity	76 µg/L (update)	89 µg/L (update)	
(Lambda-/gamma-) Cyhalothrin	ClF3CA/urine	Reduced body weight gain, acute neurotoxicity	3.9 µg/L	4.6 µg/L	
Acetamiprid	DME-ACE/urine	Developm. neurotoxicity	72 µg/L	84 µg/L	
Imidacloprid	IMI-olefin/urine	Effects on thyroid, developm. neurotoxicity	0.46 mg/L	0.53 mg/L	
Ortho-Phthalates and their substitutes					
DnBP	MnBP/urine	Reproductive toxicity	0.11 mg/L (update)	0.13 mg/L (update)	1.6 mg/L (update)
DiBP	MiBP/urine	Reproductive toxicity	0.13 mg/L (update)	0.15 mg/L (update)	2.0 mg/L (update)
BBzP	MBzP/urine	Reproductive toxicity	1.9 mg/L (update)	2.2 mg/L (update)	1.9 mg/L (update)
DEHP	Sum of 5-oxo-MEHP & 5-OH-MEHP/urine	Reproductive toxicity	0.29 mg/L (update)	0.34 mg/L (update)	
	Sum of 5-cx-MEPP & 5-OH-MEHP/urine	Reproductive toxicity	0.33 mg/L (update)	0.38 mg/L (update)	
DINP	5-cx-MEPP	Reproductive toxicity			0.36 mg/L (update)
	Sum of OH-MINP & cx-MINP/urine	Hepatic and renal effects	0.75 mg/L	0.87 mg/L	
DPHP	Sum of oxo-MPHP & OH-MPHP/urine	Effects on the thyroid	0.29 mg/L (update)	0.33 mg/L (update)	0.40 mg/L (update)
DINCH	Sum OH-MINCH & cx-MINCH/urine	Nephrotoxicity	2.7 mg/L (update)	3.2 mg/L (update)	
DEHTP	5cx-MEPTP/urine	Effects on the retina	1.6 mg/L	1.8 mg/L	
	Sum of 5cx-MEPTP & 5OH-MEHTP/urine		1.8 mg/L	2.1 mg/L	
UV filter					
DHBB	EHB/urine	General and developmental toxicity	6.7 mg/L	7.9 mg/L	
	DHB/urine		1.2 mg/L	1.3 mg/L	
	Sum of EHB&DHB/urine		7.9 mg/L	9.2 mg/L	
BP-3	Total BP-3/urine	Reproductive toxicity	0.19 mg/L	0.23 mg/L	
Metals					
Aluminium	Aluminium/urine	Cognitive impairment	20 µg/g cr	20 µg/g cr	40 µg/g cr
Soluble nickel	Ni/urine	Nasal carcinogenicity	-		12 µg Ni/L
Methyl mercury	Total Hg in hair or blood	Neurodevelopmental toxicity	3.6 mg Hg/kg hair 7 µg Hg/L blood	3.6 mg Hg/kg hair 7 µg Hg/L blood	
Elemental/inorganic mercury	Total Hg/urine	Neurotoxicity (Kidney toxicity)	7 µg Hg/L (6 µg Hg/g cr)		17 µg/L (12 µg/g cr)
Highly soluble Cr(VI) compounds	Cr/urine	Lung cancer risk level of 4:1000			EECR: 2 µg Cr/g cr (≈2.7 µg Cr/L)
Cr(VI) oxides formed under hot conditions	Cr/urine	Lung cancer risk level of 4:1000			1 µg Cr/g cr (≈1.4 µg Cr/L)
Solvents					
NMP	Sum of 5-HNMP & 2-HMSI/urine	Developmental and reproductive toxicity	9.2 mg/L	11 mg/L	
NEP	Sum of 5-HNEP & 2-HESI/urine	Reduced grasp intensity/developmental toxicity	7.7 mg/L	9 mg/L	

DnBP: di-n-butyl phthalate; MnBP: mono-n-butyl phthalate; DiBP: diisobutylphthalate; MiBP: mono-iso-butylphthalate; BBzP: butyl benzyl phthalate; MBzP: mono-benzyl phthalate; 5-OH-MEHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; 5-oxo-MEHP: mono(2-ethyl-5-oxohexyl) phthalate; 5-cx-MEPP: mono(2-ethyl-5-carboxypentyl) phthalate; DPHP: di(2-propylheptyl)phthalate, oxo-MPHP: mono(2-propyl-6-oxoheptyl) phthalate; OH-MPHP: mono(2-propyl-6-hydroxyheptyl) phthalate; DINCH: 1,2-cyclohexane dicarboxylic acid diisononyl ester; OH-MINCH: cyclohexane-1,2-dicarboxylic acid mono-hydroxyisononyl ester; oxo-MINCH: cyclohexane-1,2-dicarboxylic acid mono-oxoisononyl ester; cr: creatinine; NMP: N-methyl-2-pyrrolidone; 5-HNMP: 5-hydroxy-NMP; 5-HMSI: 2-hydroxy-N-methylsuccinimide; NEP: N-ethyl-2-pyrrolidone; 5-HNEP: 5-hydroxy-NEP; 2-HESI: 2-hydroxy-N-ethylsuccinimide.

^a Children: individuals < 18 years of age.

^b For workers, the value that is most protective for adults is shown.

^c The derivation of an HBM-GV for workers is in preparation, in this context, it will also be checked, if a further update for the HBM-GVs for the general population will be necessary.

maximum of the multiday concentration averages for most analytes (usually by less than a factor of 2). The geometric mean (GM) of the spot urine sample distribution generally under-predicted the corresponding GM of the distribution of 24-h composite samples. These observations

can assist in the interpretation of population distributions of spot samples for frequently detected analytes with relatively short elimination half-lives.

4.2. Reference parameters for biomarkers and HBM-GVs

Urinary HBM-GVs are preferably expressed per urine volume. There is currently no consensus on which parameter is most suitable as a normalisation parameter for spot urine samples to account for hydration status and the resulting different dilution of urine. For example, creatinine concentrations in the spot urine of healthy adults vary depending on gender and decrease significantly with age (Carriero et al., 2001). Also, a strong age dependency was seen for absolute daily creatinine excretion of children from the age of 3 years onward. When urinary creatinine output was adjusted for anthropometric characteristics by relating creatinine excretion to body surface area, to body weight, or to fat-free mass, a significant age dependency in creatinine excretion was seen for all 3 adjustment variables. From the age of 3 years to the oldest age group of 14–18 years, mean ratios of creatinine to body weight increased 1.4-fold and 1.5-fold in girls and boys, respectively. This was probably due to an increase in the proportion of skeletal muscle mass to body weight (Remer et al., 2002). Moreover, meat and fish consumption leads to a temporary increase of urinary creatinine excretion. If biomarker measurements in spot urine are adjusted for creatinine, this may lead to falsely lower results in omnivores, depending on the amounts of meat/fish consumed, and the time of consumption in relation to the sampling period of the urine (Abraham et al., 2023). According to the latter authors, the use of specific gravity adjustment for biomarker measurements in spot urine introduces a smaller but still obvious difference between omnivores and vegans compared to creatinine adjustment. These aspects should be considered when adjusting biomarker values in urine for creatinine and also for specific gravity. Furthermore, samples with very low or very high creatinine concentrations, defined as $< 0.3 \text{ g/L}$ ($< 2.65 \text{ mmol/L}$) or $> 3 \text{ g/L}$ ($> 26.5 \text{ mmol/L}$), should be excluded according to WHO (1996). The German HBM Commission recommended already in 2005 to report the creatinine content of urine samples as supplementary information only (HBM Commission, 2005). The publication of Middleton et al. (2019) shows that the accuracy of creatinine correction can be significantly improved using a mathematical method that takes into account the underlying excretion mechanisms; this method accounts for the discrepancy between the slope of the creatinine curve and that of the analyte.

4.3. Carcinogenic substances without effect threshold

By definition, an HBM-GV derivation requires that there is an effect threshold for the substance under consideration or its metabolites. If this is not the case, e.g. for certain carcinogenic substances, an Exposure Equivalent for Cancer Risk (EECR) can be derived. We demonstrated this under PARC for chromium VI in the workplace considering the European Commission's ACSH opinion on limit value setting for non-threshold carcinogens using a risk-based approach (ACSH, 2022). The German HBM Commission has presented in 2022 a comparable concept for the general population, according to which quantitative dose descriptors of internal exposure should be derived from those of external exposure provided that sufficient toxicokinetic information is available. Those dose descriptors of internal exposure allow the simple estimate of additional lifetime cancer risks for measured biomarker concentrations. The reverse, the indication of equivalent concentrations for selected risks, is also considered possible, but was not further elaborated (Wollin et al., 2022). The latter concept is currently in the test phase in Germany (Schettgen et al., 2026). The assessment of whether or not there is an effect threshold depends on the mechanism of action of the substance (Hartwig et al., 2020; Kobets et al., 2019). E.g., if carcinogenesis is based on direct genotoxicity, it is assumed that even the smallest amount might trigger mutation and increases the risk of carcinogenesis. Therefore, for risk assessment, a linear extrapolation of the experimental dose-response relationship to the low-dose range is generally recommended (National Research Council, 2009). Conversely, for non-genotoxic carcinogens, it is generally assumed that a threshold can be defined below which the risk is negligible and therefore the

derivation of HBM-GVs is possible.

4.4. Application of HBM-GVs

HBM-GVs are primarily intended for comparison with population-based data. This is how P05 – P95 are compared to the HBM-GVs on the European HBM Dashboard (<https://hbm.vito.be/eu-hbm-dashboard>). If individual feedback is to be given to the survey participant, this can be done in a similar manner. However, the uncertainties underlying the derivation of the HBM-GV and the limited interpretability of the measurement results with regard to various individual and health-related factors (such as lifestyle, age and genetic predisposition) must be taken into account in the communication.

If the difference between the two adult HBM-GVs derived by means of the urinary mass balance approach arises solely from sex-specific median body mass normalised 24-h urine volumes used in the calculations and not from differences in toxicological susceptibility, a single HBM-GV based on the lower of the two values can be applied for simplicity. This unified value corresponds to a more conservative percentile of body mass normalised 24-h urine volumes in men and provides a protective approach for the entire adult population. This does not, of course, apply if the point of departure for the HBM-GV derivation is based on a gender-specific critical effect.

4.5. International harmonisation of biomonitoring assessment values

In addition to the described EU PARC activity aiming to provide updated and harmonized HBM guidance values for the general population and workers, there are two further networks with overlapping responsibilities and experts working together, which enables further harmonisation: Within the OECD framework, the derivation of occupational biomonitoring levels (OBLs) is carried out to assess exposures to chemical substances, and consequently, implement risk reduction measures to reduce health risks among workers. (Hopf et al., 2024, 2025). The methods (OECD, 2022) are compatible with the methods used in PARC. As a follow-up activity, OECD effect-biomonitoring guiding principles have been developed and case study examples on mixtures were given. Biomarkers are characterized and assessed with a link to key events in adverse outcome pathways (AOPs) corresponding to endocrine disruption, genotoxicity, developmental-/neurotoxicity, and reproductive toxicity (OECD, 2025a; OECD, 2025b; Hernández et al., 2026). Knowledge transfer into an EU guidance is ongoing and led by EFSA (EFSA, 2024b).

The ISES (International Society of Exposure Science) International Human Biomonitoring (i-HBM) Working Group established 2022 the Human Biomonitoring Health-Based Guidance Value (HB2GV) Dashboard, providing an overview of biomonitoring exposure assessment values for the general population, available at: <https://www.intlexposurescience.org/i-hbm/>. Although there are many different types of HB2GVs, most of which are Biomonitoring Equivalents (BEs), Human Biomonitoring (HBM-I and HBM-II) values, and Human Biomonitoring Guidance Values (HBM-GVs). The derivation of the various HB2GVs for di-(2-ethylhexyl) phthalate (DEHP) was reconstructed to illustrate differences between available guidance values and to assist users in selecting the most suitable value. This work was carried out as a cooperation project with various actors who are entrusted with the derivation of assessment values for human biomonitoring across Europe and internationally (Macey et al., 2025). Moreover, the ISES Europe HBM working group published an overall roadmap with ten key activities in 2026 (Zare Jeddi et al., 2026).

4.6. Future perspective in derivation of HBM-GVs

Establishing more HBM-GVs will increase the role for biomonitoring to inform decisions in the interest of occupational and environmental health. If the requirement of causality and a quantified relation between

exposure and health outcome is not sufficiently supported by human data, animal studies are used to support the derivation of HBM-GVs (Apel et al., 2023). However, public concern regarding the use of animals in toxicity testing resulted in authorities demanding better justified and more responsible use of animals leading to the 3R approach (replacement, reduction, refinement) to be adopted in the design and performance of in vivo toxicity studies (Poh and Stanslas, 2024; Rosolowski et al., 2025). Nowadays, the transition to alternatives to in vivo animal testing gradually progresses leading to less use of animal models for most in vivo toxicity endpoints (ALURES). Alternative methods referred to as new approach methodologies (NAMs) will increasingly support the development of medical drugs safe for patients, as well as industrial chemicals safe for workers in their production, safe in their products and all their downstream uses.

Product safety assessments will increasingly rely on what is called QIVIVE, quantitative in vitro to in vivo extrapolation, and physiology-based biokinetic (PBK) modelling as state-of-the-art approaches to be used also in chemical safety assessments. Also, for derivation of future HBM-GVs it is expected that dose-response relationships will move in that direction (Schepers et al., 2025).

The HBM-GVs for cadmium, dimethylformamide, N,N-dimethylacetamide, bisphenol S and deoxynivalenol derived under the HBM4EU programme (Lamkarkach et al., 2021, 2022; Meslin et al., 2022; Mengelers et al., 2019; Apel et al., 2023) remain in force. The HBM-GVs for BPS will be reviewed in the second phase of the PARC project. The values for bisphenol A (Ougier et al., 2021) would need to be adjusted in line with the new EFSA TDI (EFSA CEP Panel, 2023); however, a divergence procedure is currently underway under Article 30 of Regulation (EC) No 178/2002.⁷

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Acknowledgement

This work was carried out in the framework of the European Partnership for the Assessment of Risks from Chemicals (PARC) and has received funding from the European Union's Horizon Europe research and innovation programme under Grant Agreement No 101057014. Views and opinions expressed are however those of the author(s) only

and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. Co-funding was received from the authors organizations. We would like to warmly thank comments from specialists through the national hubs of the PARC project. We would also like to thank Jens-Uwe Voss, Falco Partosch, Katharina Müller-Dott, Antje Geroßke and Rainer Konietzka for the preparation of initial working drafts for the dossiers on selected substances which were incorporated into the PARC project work.

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⁷ Report on diverging views between EFSA and BfR on EFSA bisphenol A (BPA) opinion [ema-efsa-article-30.pdf](https://www.efsa.europa.eu/en/efsajournal/doc/6848/attachment-3-download-attachment.pdf); [ema-efsa-article-30.pdf](https://www.bfr.bund.de/SharedDocs/Pressemitteilungen/DE/2023/07/bpa.html).

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