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New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission

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ABSTRACT

The German Human Biomonitoring Commission (HBM Commission) derives health-related guidance values (Human Biomonitoring assessment values, HBM values) according to the procedures described in the HBM Commission's position papers. Since the last adaption of the methodology in 2014, the HBM Commission has established a series of new HBM values, mainly on the basis of internationally agreed TDI/RfD values, or of toxicologically well- founded points of departure observed in animal studies. The derivation of these new HBM values for HBCDD, triclosan, 2-MBT, PFOA and PFOS as well as for the metabolites of glycol ethers, of Hexamoll® DINCH®, DPHP, DEHTP, NMP, NEP, and 4-MBC is specified, and the HBM values are presented together with already established HBM values for other substances. Furthermore, the HBM Commission has defined provisional reference values for 2-methoxyacetic acid and for several parabens in the urine of the German population. It has also updated provisional reference values for PCB in the blood of the German population. An overview of all available reference values is given.

Contents

Abbreviations: ADI/TDI, acceptable daily intake/tolerable daily intake; AF, assessment factor; BE, biomonitoring equivalent; BMD/BMDL, benchmark dose/benchmark dose lower bound or benchmark dose lower confidence limit; bw, body weight; DEHTP, di(2-ethylhexyl) terephthalate; DPHP, di(2-propylheptyl) phthalate or bis(2-propylheptyl) benzene-1,2-dicarboxylate; EFSA, European Food Safety Authority; fue, percentage of substance-specific metabolites eliminated with the urine in relation to the total dose of substance administered (molar basis); HBM, human biomonitoring; HBCDD, hexabromocyclododecane; Hexamoll® DINCH®, cyclohexane-1,2-dicarboxylic acid-diisononyl ester or diisononyl cyclohexane-1,2-dicarboxylate; LOAEL, lowest observed adverse effect level; 4-MBC, 3-(4-methylbenzylidene) camphor; 2-MBT, 2-mercaptobenzothiazole; NEP, *N*-ethyl-2-pyrrolidone; NMP, *N*-methyl-2-pyrrolidone; NOAEC, no observed adverse effect concentration; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PBPK/PBTK, physiologically-based pharmacokinetic/physiologically-based toxicokinetic; PCB, polychlorinated biphenyls; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid or perfluorooctane sulfonate; POD, point of departure; PTWI, provisional tolerable weekly intake; RfD, reference dose.

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1. Introduction

Human biomonitoring (HBM) implies the determination of human's internal exposure to chemicals and/or their metabolites by analysing human biological matrices, predominantly human body fluids (biomarkers of exposure). Additionally, HBM can be used to determine early effects of harmful substances (biomarkers of effect). It plays a decisive role in the monitoring of pollutants and the evaluation of the exposure of a population, of population sub-groups or individuals (Kommission HBM, 1996a). Based on the Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH), industry is responsible for the risk assessment of substances and their safety throughout the substance's life cycle. Monitoring to ensure compliance with legislation on chemical safety is the task to be accomplished by politics and the authorities providing scientific advice. Thus, HBM data can be used to assess if regulatory or voluntary measures to reduce exposure are needed. It is also of use to follow up the decrease of the population's exposure to harmful substances, i.e. those that have been banned or restricted for use.

With this paper a description is given of the science-based approaches for developing guidance values to interpret human biomonitoring data. Furthermore an overview of the up-to date guidance values is presented and the board responsible for the determination of the guidance values in Germany is introduced.

2. The HBM Commission

The HBM Commission was established in 1992 and has the mandate to support the German Environment Agency by giving advice concerning HBM related issues.

The HBM Commission's members are appointed every three years by the president of the German Environment Agency (at last in 2016). They are scientists, experts from authorities at the federal and Bundesländer (Federal States) level, universities, public health institutes and clinical institutes. In addition to regular members, permanent guests are invited, representing the Permanent Working Group of the Highest Health Authorities of the Federal States, the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety, the Federal Ministry of Health, the Robert Koch-Institute and the Federal Institute for Risk Assessment. The main fields of activity of the HBM Commission include for the appointment period 2013–2016:

- the derivation of health-related guidance values (HBM I and HBM II values),
- the description of the background exposure of the population by statistically derived reference values,
- the intensified examination of physiologically-based pharmacokinetic (PBPK) models,
- the advice for the planning and realisation of HBM studies, esp. the German Environmental Survey 2014–2017, GerES V,
- the enhancement of international cooperation for reciprocal transfer of knowledge in the field of HBM and for a comparative analysis of different evaluation methods (Kommission HBM, 2015a).

3. HBM values

Usually HBM values are derived for the general population including all sub-groups and for an assumed lifelong exposure at a corresponding level. Separate HBM values and recommendations for action are derived for particularly vulnerable population groups and/or certain phases of life (e.g. women of child-bearing age, children and the elderly) if needed. The HBM I value represents the concentration of a substance in human biological material at which and below which, according to the current knowledge and assessment by the HBM Commission, there is no risk of adverse health effects, and, consequently, no need for action. The HBM II value describes the concentration of a substance in human biological material at which and above which adverse health effects are possible and, consequently, an acute need for the reduction of exposure and the provision of biomedical advice is given.

For levels between the HBM I value and the HBM II value adverse health effects cannot be excluded any more with sufficient certainty and a follow-up examination should be performed to determine whether there is a continued elevated exposure. If repeated measurements confirm the initial result a search for potential sources of exposure should be undertaken. Exposure to such sources should be minimized or eliminated when achievable with an acceptable level of effort (Kommission HBM, 1996b).

In its new position paper, the HBM Commission describes three methods for deriving HBM values (Kommission HBM, 2014a). Firstly, HBM values can be derived on the basis of experiences with humans. Epidemiological studies providing evidence of a relationship between concentrations of a substance and/or its metabolites in human body fluids and the occurrence of adverse effects are the best fundament for the value's derivation. Secondly, HBM

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values can be established on the basis of generally accepted tolerable intake values founded for their part on studies with animals, or thirdly HBM values can be established on the basis of critical effects observed in animal experiments. To interpret the relationship between the external dose and the levels measured in body fluids and vice versa basic toxicokinetic data are necessary. In special cases the use of appropriate PBPK models (WHO IPCS, 2010) is helpful.

The urine volumes which have to be integrated in the calculation of HBM values for the matrix urine are currently reviewed to make sure that the 95th percentiles of the urine volumes of adults as well as of children are actually used.

3.1. Methods for deriving HBM values

3.1.1. Derivation based on human data

The initial concept of HBM values in environmental medicine dates back to 1996 (Kommission HBM, 1996b) and is based on epidemiological data on human toxicity. The HBM values for lead (meanwhile suspended), cadmium, mercury, thallium, polychlorinated biphenyls (PCB) and pentachlorophenol were derived according to this concept. By direct use of human data uncertainties are avoided which are connected with the extrapolation of toxicological data from animal studies to humans. Therefore, these values are the most reliable for the interpretation of the internal human exposure. However, sufficient epidemiological data to derive HBM values according to this concept are available only for a limited number of substances. This is why other methods are required in addition to derive HBM values.

3.1.2. Derivation based on a defined tolerable intake

The extension of the HBM Commission's tool box made in 2007 (Kommission HBM, 2007a,b) introduced the approach to derive HBM I values on the basis of toxicologically substantiated tolerable intake values (e.g. ADI, TDI, PTWI or comparable values) which have been determined by recognised bodies preferably at EU level, such as EFSA. The HBM I value represents the TDI equivalent and is calculated by means of toxicokinetic extrapolation. Hence, a prerequisite for the application of this method is the availability of reliable toxicokinetic information from humans. This concept was used for the first time to derive the HBM I value for the sum of the DEHP metabolites mono (2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP) and mono (2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP) in urine. In accordance with this method, also biomonitoring equivalents (BE) may be used to derive HBM I values. A BE is defined as the concentration of a chemical in blood or urine as referred to an acceptable level of exposure defined as safe in the sense of the regulation, e.g. a reference dose (RfD), or a tolerable daily intake (TDI) (Hays and Aylward, 2009; Angerer et al., 2011). A derivation of HBM II values was not envisaged in the context of this derivation method.

3.1.3. Derivation based on a critical effect seen in animal studies

The concept described above is limited due to the fact that there are no ADI, TDI or comparable values for many (mainly new) chemicals, and those chemicals which have no relevance for the uptake via food. This is why the HBM Commission has decided to develop a supplementing HBM value derivation scheme for substances for which sufficient epidemiological data or TDI values are missing. At the same time, the HBM Commission confirmed the use of the two other derivation methods as far as possible.

The extended third method for deriving HBM values is based on the identification of a critical effect using data from studies with experimental animals. Based on different points of departure (POD), HBM I and HBM II values are derived by means of assessment factors (AF) and toxicokinetic extrapolation (Kommission HBM, 2014a). Apart from establishing a TDI-like value, the same steps are applied as stipulated for the derivation of HBM I values based on the generally accepted tolerable intake (Kommission HBM, 2007a, 2007b).

a) Determination of the pivotal study

In principle, the derivation of HBM values using a POD is based on acknowledged methods for toxicological evaluation as described for example in the REACH procedure (ECHA, 2012). The aim is to work with a procedure which is as transparent, uniform, and comprehensible as possible. A first step consists in an analysis of the toxicodynamic and toxicokinetic data for the substance to be assessed. The evaluation of the data leads to the identification of the most sensitive effect endpoints and the most sensitive species. If the data are considered as sufficient for an assessment, the next step comprises the determination of the pivotal study (also referred to as the critical or reference study). In order to minimize possible uncertainties in the derivation, also human studies should be included (if available) in addition to the data from animal experiments. Such studies in humans might not be suitable or adequate in qualitative terms for deriving a HBM value based on the first method (see above), but they may serve as an additional confirmation of the risk assessment based on animal testing data and the extrapolation to humans. The pivotal study should preferably be selected from studies using the route of exposure which is decisive for humans. Possible routes of exposure include the oral and dermal uptake as well as inhalation. If two routes of exposure are identified as similarly decisive for the most sensitive adverse systemic effect in humans, a comparative toxicokinetic evaluation (e.g. on absorption, first-pass effect etc.) is required for both routes.

b) Points of departure (POD) for the derivation of HBM values

Following the selection of the pivotal study, the HBM Commission determines the POD for further derivations. Based on the final Report by the Risk Commission (Risikokommission, 2003), possible POD include:

- NOAEL,
- LOAEL, and
- Benchmark Dose

The POD may consist in an external, administered dose or an internal exposure concentration. In the majority of studies the LOAEL, or NOAEL refer to an external dose taken up by the oral route or inhalation.

In some cases, the benchmark method is used to establish toxicological parameters (Sand et al., 2008). After establishing the benchmark response (BMR), the corresponding benchmark dose (BMD) can be determined from the mathematical function. The BMD or also the unilateral lower 95% confidence interval of the BMD, referred to as BMDL (benchmark dose lower bound), can be used as POD. Regarding the probability of occurrence of an effect, the BMDL was assigned as a basis for the HBM I value, and the BMD as a basis for the HBM II value, in accordance with the definitions of HBM I and HBM II values. EFSA (2009) reported about a reanalysis of a considerable number of studies by the US National Toxicology Program (Bokkers and Slob, 2007) which found that with continuous data the BMDL05 is, on average, close to the NOAEL, if the same data set is used as a basis. Consequently, EFSA (2009) decided for using the BMDL05 as a default for the NOAEL of continuous data. Often, epidemiological studies use significantly larger data sets than studies based on animal experiments do. Therefore, a BMDL01 can be derived on the basis of such studies (EFSA, 2009, 2010). The application of the benchmark method for the derivation of HBM values has been described in detail by Schneider and Kaiser (2012) (research project 36301383 on behalf of the German Environment Agency). In any case, the choice of the method and the POD will require a scientific substantiation. Without rigid provisions, but rather in the context of an expert judgement, the HBM Commission decides on the points

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Table 1
Overview of all HBM values currently in force.

Analyte and sample material	Population group	HBM I value	HBM II value
Cadmium in urine [1998, 2011]	Children and adolescents	0.5 µg/l	2 µg/l
	Adults	1 µg/l	4 µg/l
Mercury in urine [1999]	Children and adults	7 µg/l (5 µg/g crea.)	25 µg/l (20 µg/g crea.)
Mercury in whole blood [1999]	Children and adults	5 µg/l	15 µg/l
Thallium in urine [2011]	General population	5 µg/l	/
Pentachlorophenol (PCP) in serum [1997]	General population	40 µg/l	70 µg/l
Pentachlorophenol (PCP) in urine [1997]	General population	25 µg/l (20 µg/g crea.)	40 µg/l (30 µg/g crea.)
∑DEHP metabolites 5-oxo- and 5-OH-MEHP in urine [2007]	Children aged 6–13	500 µg/l	/
	Women of child-bearing age	300 µg/l	
	Men aged 14 and older as well as remaining general population	750 µg/l	
Bisphenol A in urine [2012, updated 2015]	Children	0.1 mg/l	/
	Adults	0.2 mg/l	
∑ of PCB (138 + 153 + 180) in serum × 2 [2012]	Infants, small children and women of child-bearing age	3.5 µg/l	7 µg/l
Glycolether which are metabolized to 2- methoxyacetic acid (MAA), urine [2014]	General population	0.4 mg MAA/g creatinine	1.6 mg MAA/g creatinine
Glycolether which are metabolized to 2- ethoxyacetic acid (EAA), urine [2016]	Adults	5 mg EAA/l	/
∑ DINCH® metabolites OH-MINCH and cx-MINCH in urine [2014]	Children	3 mg/l	/
	Adults	4.5 mg/l	
∑ DPHP metabolites OH-MPHP and oxo- MPHP in urine [2015]	Children	1 mg/l	/
	Adults	1.5 mg/l	
DEHTP metabolite 5cx-MEPTP in urine (publication in preparation)	Children	1.8 mg/l	/
	Adults	2.8 mg/l	
Hexabromocyclododecane (HBCD(D)) [2015]	General population	0.3 µg/g lipid (1.6 µg/l blood plasma)	/
∑ *N*-methyl-2-pyrrolidone metabolites 5-hydroxy-NMP and 2-hydroxy-N-methylsuccinimide in urine [2015]	Children	10 mg/l	30 mg/l
	Adults	15 mg/l	50 mg/l
∑ *N*-ethyl-2-pyrrolidone metabolites 5-hydroxy-NEP and 2-hydroxy-N-ethylsuccinimide in urine [2015]	Children	10 mg/l	25 mg/l
	Adults	15 mg/l	40 mg/l
Triclosan in urine [2015]	Children	2 mg/l	/
	Adults	3 mg/l	
2-mercaptobenzothiazole (2-MBT) in urine [2015]	Children	4.5 mg/l	/
	Adults	7 mg/l	
∑ 3-(4-methylbenzylidene) camphor metabolites 3-4CBHC and 3-4CBC in urine [2016]	Children	0.3 mg/l	/
	Adults	0.5 mg/l	
PFOA in blood plasma [2016]	General population	2 µg/l	/
PFOS in blood plasma [2016]	General population	5 µg/l	/

of departure for further derivation on the basis of the data available, the dose-effect curve, the toxicological mechanisms, and the severity and type of effect. The POD that served as a basis for deriving DNELs (derived no effect levels) in the context of the REACH procedure may be used for deriving HBM values if all eligible studies have been published, and both the selection procedure and the methods of derivation have been made public and transparent.

In cases where no studies are available on the main route of exposure, studies on other routes may also be used in combination with a route-to-route extrapolation. This requires a POD which refers to an adverse systemic effect of the substance. A prerequisite for a route-to-route extrapolation consists in the similarity of the critical effects and of the toxicokinetics for the routes of exposure concerned (Rennen et al., 2004; IGHRC, 2006).

c) Use of assessment factors (AF)

After the critical study and the POD for deriving the HBM I and HBM II values have been determined, the assessment factors have to be selected.

The HBM Commission has agreed to use the assessment factors determined by consensus in the ECHA Guidance Document R.8 (ECHA, 2012). The choice and magnitude of assessment factors have to be justified in individual cases.

The assessment factors are intended to take account of the following differences and uncertainties: LOAEL vs. NOAEL, duration adjustment (time scaling), study duration adjustment (minimum: subchronic study), interspecies differences, intraspecies differences, and other uncertainties (type of effect, severity of effect, quality of data available).

If the POD represents a NOAEL or LOAEL, also the severity of the toxic effect at the next higher dose level and the spacing of doses used have to be taken into account for a reasonable evaluation. This can be done by applying an additional assessment factor.

d) Taking into account the data quality

Generally, the derivation of HBM values is based on data published in peer-reviewed scientific journals. The description of the study conditions and the range of reported parameters are important criteria for evaluating the data quality. The HBM Commission evaluates the quality of the initial or pivotal study by using the Klimisch criteria (Klimisch et al., 1997).

4. New HBM values for emerging substances

An overview of all available HBM values is given in Table 1.

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4.1. HBM values for glycol ethers

4.1.1. HBM values for glycol ethers which are metabolized to 2-methoxyacetic acid (MAA)

Glycol ethers which are metabolized to alkoxyacetic acids are substances of very high concern because of their repro-, hemato-, and neurotoxic effects. The biological monitoring of MAA is generally accepted for the quantitative detection of exposure to ethylene glycol monomethyl ether (EGME), ethylene glycol monomethyl ether acetate (EGMEA), and ethylene glycol dimethyl ether (EGDME). For the exposure of the general population inhalation and dermal absorption are relevant. The HBM Commission used a benchmark dose relating to teratogenic effects in rabbits (Hanley et al., 1984a,1984b) as POD for the derivation of HBM values. On this basis a HBM I value of 0.4 mg MAA/g creatinine and a HBM II value of 1.6 mg MAA/g creatinine have been derived. Especially for pregnant women exposures at and above the HBM II value give reasons for concern. Risk management can be done by air measurements to determine and, if required, avoid the source of exposure. The use of cleaning supplies and cosmetic products should also be traced and reduced if applicable (Kommission HBM, 2014b).

4.1.2. HBM I value for glycol ethers which are metabolized to 2-ethoxyacetic acid (EAA)

Ethylene glycol ethyl ether (EGEE) and ethylene glycol ethyl ether acetate (EGEEA) are, as other glycol ethers, excellent solvents for water and many organic substances. They are used amongst others for the production of paints, lacquers, and cleaning agents. The general population might be exposed via inhalation and dermal absorption. It is assumed that the metabolite EAA is responsible for the toxic effects of EGEE and EGEEA on hematopoiesis and reproduction (Welsch, 2005). The NOEL of 50 ppm for fetotoxicity and fetal defects in rats and rabbits (Doe, 1984) has been determined as POD. According to the PBTK extrapolation of Gargas et al. (2000) maternal EAA blood concentrations that equal those at the NOEL for rats are given, if pregnant women are exposed to 25 ppm of ethylene glycol ethyl ether (EGEE) for 8 h/day, 5 days/week. This corresponds to an average weekly exposure of 6.0 ppm (25 ppm × 8/24 × 5/7), or 22.1 mg EGEE/m^3. With an alveolar ventilation rate of Qalv = 7.9 m^3/day (for a 60 kg woman), a daily intake of 175 mg EGEE, or 2.91 mg EGEE/kg bw/day is equivalent to the NOEL.

Taking into account the inter-individual variability, studied by Sweeney et al. (2001), an assessment factor of 1.8 for toxicokinetics has to be applied together with an AF of 3.2 for the toxicodynamic intraspecies variability and an AF of 2.5 for the toxicodynamic interspecies variability (total AF of 14.4) to get a TDI-like value of 0.2 mg EGEE/kg bw/day.

With a molar-based fue of 0.42, a Fmol in mg EAA/mg EGEE of 1.2 and an urine volume of adults of 0.02 l/kg bw/day the HBM I value for adults was calculated as follows: 0.2 × 0.42 × 1.2: 0.02 = 5 mg EAA/l urine. This HBM I value applies to the joint exposure to EGEE and EGEEA (Kommission HBM, 2016a).

Since the whole body was exposed to EGEE in the animal study, and rodent skin is nearly always more permeable to solvent vapour than human skin, the dermal uptake of vapour is inherent in the rat NOEL value (Sweeney et al., 2001).

4.2. HBM I values for the sum of Hexamoll® DINCH® metabolites OH-MINCH and cx-MINCH

Hexamoll® DINCH® (cyclohexane-1,2-dicarboxylic acid-diisononyl ester or diisononyl cyclohexane-1,2-dicarboxylate) is a plasticiser used in plastic articles. It was developed as a substitute for bis(2-ethylhexyl) phthalate (DEHP) which has been shown in animal studies to be toxic for reproduction (Cat. 1B). DINCH has, according to the current state of knowledge, more favourable toxicological properties. In contrast to DEHP it was neither toxic as to fertility nor as to development in animal studies. DINCH is used in sensitive applications such as toys (Janssen and Bremmer, 2009) or medical devices (SCENIHR, 2008). DINCH is approved for the use in plastic materials for food packaging (Regulation (EU) No 1935/2004) and has also been listed in Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food without a specific migration limit (FCM substance No. 775). According to the manufacturer, the production volume was 200,000 t per year in 2014. Biomarkers for measuring DINCH include oxidation products of the alkyl side chain of the monoester MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester (OH-MINCH), cyclohexane-1,2-dicarboxylic acid-mono(carboxy-isooctyl) ester (cx-MINCH) and cyclohexane-1,2-dicarboxylic acid-mono(oxo-isononyl) ester (oxo-MINCH). Because oxo-MINCH has been predominantly described in semi-quantitative terms, and only recently an analytical standard has been developed synthetically, the focus has so far been on the analysis of OH-MINCH and cx-MINCH. These two biomarkers differ considerably regarding their elimination half-life. Analysis is performed after enzymatic hydrolysis by means of an on-line HPLC–MS/MS method. Quantification by isotope dilution leads to LOQ (limit of quantification) values for the oxidized metabolites close to 0.05 μg/l (Schütze et al., 2012).

For the derivation of the HBM I values the following parameters were used:

- TDI value: 1 mg/kg bw/day (EFSA, 2006),
- quotient of the averaged molecular weight of the metabolites and the molecular weight of DINCH: 0.75,
- urinary excretion factor (fue(48 h)): 0.1276 for both metabolites (Koch et al., 2013),
- volume of urine, children: 0.03 l/kg bw/day,
- volume of urine, adults: 0.02 l/kg bw/day.

4.2.1. Calculation of HBM I values (urine)

HBM I (OH-MINCH + cx-MINCH) children: 1 × 0.75 × 0.1276/0.03 = 3.190, *rounded* 3 mg/l

HBM I (OH-MINCH + cx-MINCH) adults: 1 × 0.75 × 0.1276/0.02 = 4.785, *rounded* 4.5 mg/l (Kommission HBM, 2014d)

First results of the analysis of DINCH metabolites in 24 h urine samples from the German Environmental Specimen Bank show that the body burden of the test persons was well below the HBM I value in 2012 (Schütze et al., 2014).

4.3. HBM I values for the sum of DPHP metabolites oxo-MPHP and OH-MPHP

DPHP (di(2-propylheptyl) phthalate or bis(2-propylheptyl) benzene-1,2-dicarboxylate) is a plasticiser for plastic materials and was developed as a technological alternative to diisodecyl phthalate (DIDP). These two phthalates differ in the structure of their side chains. The DPHP side chain is largely based on 2-propylheptane-1-ol, other components of the side chain include 4- and 5-methyl-2-propylhexane-1-ol. Due to its low volatility, DPHP is mainly used in soft PVC articles such as roofing and covering tarpaulins, cable and wire insulation materials as well as vehicle interior furnishings. So far, no assessment by the European Food Safety Authority, EFSA, is available for DPHP. Consequently, DPHP is not listed under Regulation (EU) No. 10/2011 and therefore, cannot be used in the food sector. Biomarkers of exposure are oxo-MPHP (oxo-mono(propylheptyl) phthalate, fue: 13.5%) and OH-MPHP (hydroxy-mono(propylheptyl)phthalate, fue: 10.7%) (Leng et al., 2014). The elimination of metabolites was tested in male subjects. Neither age-specific differences nor a dependency, if any, of the

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metabolism on the level of exposure were examined until now. For the analysis of DPHP metabolites in human urine a newly developed specific method is available that is described in detail elsewhere (Gries et al., 2012). The limit of detection for the metabolites is between 0.05 and 0.1 μg/l and the limit of quantification is between 0.15 and 0.3 μg/l. For the derivation of the HBM I values the HBM Commission selected a subchronic feeding study with rats as pivotal study (BASF, 1995), showing a NOAEL of 39 (rounded 40) mg/kg bw/day. The relevant effects are those on the thyroid and the pituitary gland (BfR, 2011). Taking into account a total assessment factor of 200 (2 for the adjustment of the study duration: subchronic → chronic, 10 for the intraspecies variability, and 10 for the interspecies variability), a safe external exposure (TDI-like value) of 0.2 mg/kg bw/day can be assumed.

For the derivation of the HBM I values the following parameters were used:

- TDI-like value: 0.2 mg/kg bw/day,
- ratio of the averaged molecular weight of the metabolites to the molecular weight of DPHP: 0.72,
- urinary excretion factor (fue(48 h)): 0.24 for the metabolites oxo- and OH-MPHP,
- volume of urine, children: 0.03 l/kg bw/day,
- volume of urine, adults: 0.02 l/kg bw/day.

4.3.1. Calculation of HBM I values (urine)

HBM I (oxo- + OH-MPHP), children: $0.2 \times 0.72 \times 0.24/0.03 = 1.152$ mg/l *(rounded:* 1 mg/l)

HBM I (oxo- + OH-MPHP), adults: $0.2 \times 0.72 \times 0.24/0.02 = 1.728$ mg/l *(rounded:* 1.5 mg/l) (Kommission HBM, 2015b).

4.4. HBM I values for the DEHTP metabolite 5cx-MEPTP

Di(2-ethylhexyl) terephthalate or bis(2-ethylhexyl) terephthalate (DEHTP) is used as plasticiser for PVC products and substitutes increasingly other plasticisers which are classified as toxic to reproduction. Within the framework of REACH-registration DEHTP counts as high production volume chemical with a total tonnage of 10,000–100,000 tpa. It is, according to currently available data, not genotoxic or carcinogenic (ECHA, 2016). DEHTP did not show antiandrogenic properties (Furr et al., 2014), and no reproductive toxicity could be seen in animal studies (ECHA, 2016). The peroxisome proliferating potential has been reported to be very weak (ECHA, 2016). The European Food Safety Authority (EFSA, 2008) derived a TDI value of 1 mg/kg bw/day based upon a 2-year combined toxicity/carcinogenicity study (Deyo, 2008); the most sensitive endpoints observed were effects on the retina and the nasal turbinates.

The HBM Commission based its derivation of the HBM I values for DEHTP also onto the endpoint "effects on the retina" but used instead of the NOAEC the BMDL10 of 54 mg/kg bw/day, as NSF International (2012) did for its derivation of an oral RfD. A factor of 10 each to account for intraspecies and interspecies variability was selected to receive a TDI-like value of 0.54 mg/kg bw/day. An additional factor of 3 used by NSF International (2012) for database deficiencies was not considered necessary. For the purpose of human biomonitoring a new sensitive HPLC–MS/MS method with online sample clean-up and isotope dilution (Lessmann et al., 2016a,b) has been established. The limit of quantification is 0.2 μg/l for 5cx-MEPTP (1-mono(2-ethyl-5-carboxyl-pentyl) benzene-1,4 dicarboxylate), the main specific urinary metabolite of DEHTP on which human biomonitoring should rely on.

5cx-MEPTP represented in an oral study with three volunteers about 13% (48 h, mean) of the applied dose in urine, followed by 5OH-MEHTP (mean: 1.8%), 5oxo-MEHTP (mean: 1.0%) and 2cx-MMHTP (0.3%) (Lessmann et al., 2016a,b).

For the derivation of the HBM I values the following parameters were used:

- TDI-like value: 0.54 mg/kg bw/day,
- ratio of the molecular weight of the metabolite 5cx-MEPTP to the molecular weight of DEHTP: 308.33/390.56 = 0.79
- urinary excretion factor (fue(48 h)): 0.1295 for the metabolite 5cx-MEPTP
- volume of urine, children: 0.03 l/kg bw/day,
- volume of urine, adults: 0.02 l/kg bw/day.

4.4.1. Calculation of HBM I values (urine)

HBM I (5cx-MEPTP), children: $0.54 \times 0.79 \times 0.1295/0.03 = 1.84$ mg/l *(rounded:* 1.8 mg/l*)*

HBM I (5cx-MEPTP), adults: $0.54 \times 0.79 \times 0.1295/0.02 = 2.76$ mg/l *(rounded:* 2.8 mg/l) (publication projected).

4.5. HBM I value for HBCDD

Hexabromocyclododecane (HBCDD) has up to now mainly been used as flame retardant in thermal insulation foams and in textile coatings. Evidence is provided that HBCDD occurs in house dust, mother milk, human blood, and fatty tissue. EFSA (2011) identified neurodevelopmental effects on behaviour as the critical endpoint of toxicological studies, and derived a benchmark dose lower confidence limit for a benchmark response of 10% (BMDL10) of 0.93 mg/kg bw (single oral administration of HBCDD as a mixture of the three diastereoisomers alpha, beta, and gamma HBCDD). In accordance with the EFSA Panel on Contaminants in the Food Chain (2011) the HBM Commission considers the study of Eriksson et al. (2006) as key study and the resulting BMDL10 as POD for the derivation of the HBM I value. The available toxicokinetic data suggest that orally administered HBCDD is easily absorbed and accumulates in lipid tissue. Because the elimination kinetics of HBCDD in rodents and humans differ, external dose levels of HBCDD associated with toxic effects in animals cannot be simply extrapolated for the risk assessment in humans. Instead, the internal body burden provides a more appropriate dose metric for a direct comparison of effects in animals and humans. On the basis of a proven oral absorption in rodents of 85%, the body burden at the BMDL10 is 0.79 mg/kg bw. This value of 0.79 mg/kg bw has to be divided by a factor of 0.32 (women: 32% fatty tissue) to receive the tolerable internal dose for the lipid compartment of the body. With a total AF of 8 for differences in toxicodynamics (intraspecies factor = 3.2, interspecies factor = 2.5) the HBM I value for total HBCDD was finally set at 0.3 μg/g lipid (1.6 μg/l plasma) (Kommission HBM, 2015c).

4.6. HBM values for the sum of NMP metabolites 5-HNMP and 2-HMSI

N-methyl-2-pyrrolidone (NMP) is used as a solvent in many technical applications. The general population may be exposed to NMP from the use as ingredient in paint and graffiti remover, indoors also from the use in paints and carpeting. Because of its developmental toxicity, NMP is classified as substance of very high concern and is listed as candidate for authorisation under REACH (ECHA, 2013; National Institute for Public Health and the Environment (RIVM), 2013). The developmental effects are also considered as the critical effects for the HBM value derivation. The NOAEL of 125 mg/kg bw/day of an oral study on developmental toxicity with rats (Saillenfait et al., 2002) was chosen as POD and a total assessment factor of 300 was applied to calculate a tolerable external dose or TDI-like value of 0.42 mg/kg bw/day (AF 10 for intraspecies variability, AF 10 for interspecies variability, and AF 3 as additional factor having regard to the results of a second study (Sitarek et al., 2012)). 5-Hydroxy-NMP (5-HNMP) and

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2-hydroxy-N-methylsuccinimide (2-HMSI) were identified as main metabolites in urine and their excretion is used to estimate the internal exposure with NMP.

For the derivation of the HBM values the following parameters were used:

- TDI-like value: 0.42 mg/kg bw/day,
- ratio of the averaged molecular weight of the metabolites and the molecular weight of NMP: 1.23,
- urinary excretion factor (fue): 0.65 for the metabolites 5-HNMP and 2-HMSI (Åkesson and Jönsson,1997),
- volume of urine, children: 0.03 l/kg bw/day,
- volume of urine, adults: 0.02 l/kg bw/day.

4.6.1. Calculation of HBM values (urine)

HBM I (5-HNMP+2-HMSI), children: $0.42 \times 1.23 \times 0.65/0.03 = 11.2$ mg/l *(rounded:* 10 mg/l)

HBM I (5-HNMP+2-HMSI), adults: $0.42 \times 1.23 \times 0.65/0.02 = 16.8$ mg/l *(rounded:* 15 mg/l)

The HBM II values were set at 30 mg/l for children and 50 mg/l for adults (Kommission HBM, 2015d).

4.7. HBM values for the sum of NEP metabolites 5-HNEP and 2-HESI

N-ethyl-2-pyrrolidone (NEP), a polar aprotic solvent, is used in many applications as substitute for the structural analogue *N*-methyl-2-pyrrolidone (NMP), e.g. for surface coatings, in cleaning agents and paint strippers. Inhalation can be assumed to be the most important route of exposure, followed by the dermal route. Monitoring studies indicate that individuals within the general public, without occupational exposure, may be exposed to NEP to an extent which is comparable to NMP (Käfferlein et al., 2013). Exposure to NEP can be quantified by determining the excretion of its urinary metabolites 5-hydroxy-*N*-ethyl-2-pyrrolidone (5-HNEP) and 2-hydroxy-*N*-ethylsuccinimide (2-HESI) (Koch et al., 2014). A specific method already available for the analysis and quantification of NEP metabolites in urine (Schindler et al., 2012) has been enhanced for the biomonitoring of the general population: following solid phase extraction, separation is performed by gas chromatography, and the detection is carried out by using tandem mass spectrometry with quantification via isotope dilution. Both for 5-HNEP and 2-HESI, the limit of detection (LOD) is 1 μg/l, and the limit of quantification (LOQ) is 2.5 μg/l (Bader et al., 2014).

For the derivation of the HBM values, the HBM Commission evaluated different studies and toxicological endpoints. Finally the HBM Commission decided on a subchronic feeding study with rats as pivotal study (Kaspers et al., 2006) and on the BMDL05 and the BMD10 for the endpoint "reduced grasp intensity" as points of departure (POD). With a total assessment factor of 200 (2 for study duration adjustment, 10 for intraspecies variability, and 10 for interspecies variability) the following values were received:

$BMDL_{05}$ as POD for HBM I: 90 mg/kg bw/day → 0.45 mg/kg bw/day (TDI-like value)

BMD_{10} as POD for HBM II: 250 mg/kg bw/day → 1.25 mg/kg bw/day

For the derivation of the HBM values the following parameters were used:

- TDI like value: 0.45 mg/kg bw/day,
- value for HBM II value derivation: 1.25 mg/kg bw/day,
- ratio of the averaged molecular weight of the metabolites and the molecular weight of NEP: 1.2,
- urinary excretion factor (fue(96 h)): 0.505 for the metabolites 5-HNEP and 2-HESI (Koch et al., 2014),
- volume of urine, children: 0.03 l/kg bw/day,
- volume of urine, adults: 0.02 l/kg bw/day.

4.7.1. Calculation of HBM values (urine)

HBM I (5-HNEP+2-HESI) children: $0.45 \times 1.2 \times 0.505/0.03 = 9.09$ mg/l *(rounded:* 10 mg/l)

HBM I (5-HNEP+2-HESI) adults: $0.45 \times 1.2 \times 0.505/0.02 = 13.64$ mg/l *(rounded:* 15 mg/l)

HBM-II (5-HNEP+2-HESI) children: $1.25 \times 1.2 \times 0.505/0.03 = 25.25$ mg/l *(rounded:* 25 mg/l)

HBM-II (5-HNEP+2-HESI) adults: $1.25 \times 1.2 \times 0.505/0.02 = 37.88$ mg/l *(rounded:* 40 mg/l)

The HBM I values refer to the endpoint "reduced grasp intensity" but are also protective for developmental toxicity. Measurements at and above the HBM II value give cause for concern, especially for pregnant women. Air measurements to detect and eliminate the source of exposure can be useful. The possibility of skin absorption from use of cleaning agents and paint strippers should also be traced. The values apply to the evaluation of single substances. In practice, it has to be assumed that exposure to NEP may always occur simultaneously with and in addition to NMP. Due to the very similar toxicological profiles of these two substances, in particular regarding developmental toxicity and teratogenic effects, a mixed exposure to both substances has to be taken into account in the evaluation of findings (Kommission HBM, 2015e).

4.8. HBM I values for triclosan

Triclosan is a lipophilic, broad spectrum antimicrobial agent which is used in many personal care products like toothpaste, shower gel, and in consumer products like textiles and toys. The HBM I value for triclosan is based on the BE value derivation for triclosan (Krishnan et al., 2010). The NOAEL of 12 mg/kg bw/day used as POD for the calculation of both, the BE and the HBM I value, is obtained from an oral study over 2 years with rats (DeSalva et al., 1989) and refers to the endpoints haematotoxicity and decrease in spleen weight. The NOAEL has been confirmed by the Scientific Committee on Consumer Safety of the European Commission (SCCS) in 2011. Application of a total assessment factor of 100, multiplication with the fue of 0.54 (Sandborgh-Englund et al., 2006) and division by the value for the urine volume of 0.02 l/kg bw/day (adults) or 0.03 l/kg bw/day (children) leads to HBM I values of 3.2 mg triclosan/l for adults and 2.2 mg triclosan/l for children (Kommission HBM, 2015f).

For the period of 1995–2012 the time trend of triclosan in the urine of the German general population was established by analysing 660 urine samples of the German environmental specimen bank from the years 1995, 1997, 1999, 2001, 2003, 2005, 2006, 2007, 2008, 2009 and 2012. The samples came predominantly from students of the university of Münster aged 20–30. From each year 30 samples of males and 30 samples of females were analysed. Triclosan could be detected in all 660 samples measured. No differences between males and females could be determined. The median concentration of Triclosan in urine ranged from 0.50 μg/l to 3.20 μg/l for each separate year. A time trend was not detectable for the survey period, although a voluntary waiver declaration of the producers exists (Kommission HBM, 2015f).

4.9. HBM I values for 2-mercaptobenzothiazole (2-MBT)

2-Mercaptobenzothiazole (2-MBT) is mainly used as a vulcanisation accelerator in the production of rubber. Other applications are as a fungicide in paints and varnishes as well as for the external treatment of animals. Because of its manifold applications in consumer products, for example in soothers, exposure of the

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general population to 2-MBT can't be excluded. For the toxicological evaluation of a possible body burden the HBM Commission derived HBM I values for 2-MBT in the urine of children and adults. The no observed adverse effect level of 94 mg/kg bw/day from a subchronic oral study with mice was used as POD (NTP (National Toxicology Program), 1988; SCF, 2000; BfR, 2008). The relevant endpoint for this value was the increased liver weight. After consideration of a total assessment factor of 350 (2 for study duration adjustment: subchronic to chronic, 10 for intraspecies variability, and 17.5 for interspecies variability), a tolerable daily intake of 0.3 mg/kg bw/day was deduced for humans. Having furthermore regard to the percentage of 2-MBT and its glucuronide excreted in urine (45%) and the body weight proportional urine volume, the following HBM I values could be derived:

HBM I (children): 4.5 mg *2-MBT/l urine,*
HBM I (adults): 7 mg *2-MBT/l urine* (Kommission HBM, 2015g).

4.10. HBM I values for the sum of 4-MBC metabolites 3-4CBHC and 3-4CBC

The substance 3-(4-methylbenzylidene) camphor (4-MBC, CAS-No. 36861-47-9 as well as 38102-62-4) is used as UV-filter in cosmetics, mainly in sunscreen lotions. National as well as European evaluations are available for the substance, especially from the Scientific Committee on Consumer Products (SCCP, 2008). The SCCP did not derive a TDI value, but used for a margin of safety (MoS) assessment a NOAEL of 25 mg/kg bw/day based on effects on the thyroid gland of rats in a subchronic oral study (Kieser et al., 1984). Newer studies, however, indicate lower NOAEL values (Maerkel et al., 2007; Durrer et al., 2007; Hofkamp et al., 2008; Schlumpf et al., 2008; Faass et al., 2009). The HBM Commission focused on the one generation study with rats of Durrer et al. (2007) which resulted in a NOAEL of 0.7 mg/kg bw/day, corresponding to a tolerable daily intake of 0.01 mg/kg bw. Humans excrete 80% of the available systemic proportion of administered 4-MBC in the urine whereupon 80% are assigned to the main metabolite 3-(4-carboxybenzylidene)-6-hydroxycamphor (3-4CBHC) and 20% to 3-(4-carboxybenzylidene) camphor (3-4CBC). A sensitive method for the analysis of these metabolites in urine has been developed with LOQs of 1 μg/l for 3-4CBHC and 1.5 μg/l for 3-4CBC. The HBM Commission established for the metabolite 3-4CBHC HBM I values of 0.38 mg/l urine for adults and 0.25 mg/l urine for children. The HBM I values for 3-4CBC were set at 0.09 mg/l urine for adults and 0.06 mg/l urine for children.

The rounded HBM I values for the sum of the metabolites 3-4CBHC and 3-4CBC are accordingly 0.5 mg/l *urine for adults and* 0.3 mg/l *urine for children* (Kommission HBM, 2016b).

4.11. HBM I values for perfluorooctanoic acid (PFOA) und perfluorooctanesulfonic acid (PFOS) in blood plasma

Based on an assessment of the literature on human epidemiological studies and on animal studies the HBM Commission decided to set HBM I values for PFOA and PFOS in blood plasma at 2 ng PFOA/ml and 5 ng PFOS/ml (Kommission HBM, 2016c, detailed publication in preparation).

The method chosen for the HBM I value derivation rests upon human data and critical effects. Epidemiological studies point, for instance, to an association between the exposure to PFOA or PFOS and risks of delayed fertility or also of infertility. Taking the reported upper values of the quantiles without significant effects each as POD the resulting values for PFOA are constantly below 5 ng/ml plasma, with a trend to 2 ng/ml (Fei et al., 2009; Whitworth et al., 2012; Vélez et al., 2015). Estimates for PFOS are below 30 ng/ml plasma, in the lowest case at 17 ng/ml (Fei et al., 2009; Whitworth et al., 2012). Recently, a meta-analysis was published which shows a significant link between fetal growth and exposure to PFOA (Johnson et al., 2014). Furthermore, Fitz-Simon et al. (2013) observed in a longitudinal study an association of raised cholesterol concentrations with increasing PFOA or PFOS exposure. Geiger et al. (2014) concluded from their studies among US children and adolescents at the age of 6–18 years that the increasing internal exposure to PFOA or PFOS is significantly associated with the total cholesterol and LDL-cholesterol (POD for PFOA: 4.7 ng/ml, POD for PFOS: 22 ng/ml). In addition, the immune response can be impaired. Grandjean and Budtz-Jørgensen (2013) found with their benchmark dose-modelling associations of a PFOA or PFOS exposure at a very low level and a decreased immune response of children which were vaccinated with Tetanus or Diphtheria (POD for PFOA: 0.3 ng/ml (BMDL5), POD for PFOS: 1.3 ng/ml (BMDL5)).

Analogies between animal and epidemiological studies enhance the plausibility that the effects chosen as endpoints are relevant. Thus, mammary epithelial growth has turned out to be a very sensitive marker of developmental toxicity for the offspring of orally PFOA-treated mouse dams. Inhibitory effects have been observed at 285 ng PFOA/ml blood serum (LOAEL) (Macon et al., 2011). Assuming an assessment factor of 10 to extrapolate from LOAEL to NOAEL, a corresponding NOAEL would be in the range of 29 ng PFOA/ml serum. Extrapolated to humans does that mean that no effects on the sexual differentiation have to be anticipated up to a concentration of 1 ng/ml serum. PFOS suppresses the humoral immunity in male mice at very low doses. Peden-Adams et al. (2008) reported a LOAEL of 1.66 μg PFOS/kg body weight (oral dose). The blood concentration in these animals was 91.5 ng PFOS/g serum. The NOAEL was about 10 times lower, the corresponding blood concentration was 17.8 ng PFOS/g serum. In female mice, the NOAEL was about 20-fold higher compared to the male animals. Extrapolated to humans does that mean that no effects on the immune system have to be expected at a concentration of 1–10 ng/ml serum.

In summary, the HBM Commission rates effects in the subsequent areas as well proven, relevant, and significantly associated with an exposure to PFOA and/or PFOS:

1. Fertility and pregnancy
   a) Time to wanted pregnancy
   b) Waiting period for pregnancies > 1 year
   c) Gestosis and gestational diabetes
2. Weight of newborns at birth
3. Lipid metabolism
4. Immunity after vaccination, immunological development
5. Hormonal development, age at puberty/menarche
6. Thyroid metabolism
7. Onset of menopause

The literature reports quantile contrasts, BMD derivations or regression analyses for continuous endpoints (e.g. birth weights, fat metabolism, sex hormones) differently. Regarding quantile contrasts, the HBM Commission has selected the upper bounds of the quantiles without significant effects. This is in line with the approach of the HBM I value, marking a level of protection at which "adverse health effects are not expected". BMD modelling usually leads to lower POD, but cannot be carried out consistently with the available data.

The Commission points out that the sample sizes and concentration ranges reported in different studies as well as the chosen quantiles and confounders cannot be evaluated using a standard procedure. The Commission has therefore decided to use the resulting POD ranges as a basis for deriving the HBM I value.

The data available do not appear to show proof of genotoxicity of PFOA and PFOS.

Results of the analysis of 258 cryo-conserved plasma samples of the German environmental specimen bank (age group 20–29

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years) allow a comparison with the derived HBM I values and reflect how far voluntary and regulatory mitigation measures took effect until 2010 (Schröter-Kermani et al., 2013). Since 1986 the median of the PFOA concentration had been fluctuating between 4.8 and 6.3 ng/ml before it decreased in 2008. After an increase from 1982 to 1986, the median of the PFOS concentration leveled off at 20-24 ng/ml until the late 1990s. Since 2001 the median of the PFOS concentration had been decreasing continuously to 4 ng/ml in 2010. Further data on the exposure of children (aged between 3 and 17) to PFOA and PFOS are being collected in the context of the current German Environmental Survey 2014–2017, GerES V.

5. Reference values

In order to be able to describe the background exposure of the population and its temporal development the HBM Commission derives reference values by means of statistical methods. These reference values are based on the 95% confidence interval of the 95th percentile of the concentration of a chemical substance in the matrix obtained from a reference population. Preferably, reference values are derived from data obtained from a representative population sample in the context of the German Environmental Survey, GerES. They allow a uniform assessment of the body burden at the German national level, and are indispensable to demonstrate whether a certain exposure level exceeds the background exposure level, e.g. accident-related exposures. Because of their statistical nature, reference values cannot serve to asses health risks. Reference values are checked continuously and are updated if new information becomes available.

Table 2
Provisional reference values (RV_{95}) for parabens in urine (Kommission HBM, 2014c).

Parameter	Population group	RV_{95}
Methylparaben	Women	400 µg/l
	Men	240 µg/l
Ethylparaben	Women	50 µg/l
	Men	25 µg/l
Propylparaben	Women	100 µg/l
	Men	50 µg/l
Butylparaben	Women	20 µg/l
	Men	10 µg/l
Isobutylparaben	Women	10 µg/l
	Men	3 µg/l

During the last 3 years the HBM Commission defined provisional reference values for MAA (0.3 mg MAA/l) (Kommission HBM, 2014b) and for several parabens (Table 2, Kommission HBM, 2014c) in the urine of the German population.

Parabens are the alkyl-, isoalkyl-, and benzylester of 4-hydroxybenzoic acid and their sodium salts. They are used predominantly as preservatives. With the exception of the data from the German environmental specimen bank, the sample size of available data sets is too small for a reliable determination of the 95% quantiles. This is why reference values for females and males were derived on the basis of the data from the German environmental specimen bank. These reference values are provisional ones because they are lacking representativeness with regard to the selection of test persons and a regional and demographic stratification. The data pool of the German environmental specimen bank comprises 660 data sets (referring to 24 h urine) with balanced sizes of sex groups (N = 330 each). The test person's age varied between

Table 3
Provisional reference values (RV_{95}) for PCB in blood.

Previous values				update					
Parameter	Population/Age group [years]	Year of the study	RV_{95} in µg/l whole blood	Year of the study	Men/Women µg/l whole blood	Men µg/l plasma	Women µg/l plasma	Men µg/g lipid	Women µg/g lipid
PCB 138	7–14[a]	2003/06	0.3						
	18–19[b]	1997/99	0.4	2010[c]	0.13	0.24	0.22	0.035	0.032
	20–29[b]	1997/99	0.6	2010[c]	0.20	0.36	0.33	0.052	0.048
	30–39[b]	1997/99	0.9	2010[c]	0.45	0.82	0.75	0.12	0.11
	40–49[b]	1997/99	1.4	2010[c]	0.70	1.3	1.2	0.18	0.17
	50–59[b]	1997/99	1.7	2010[c]	0.85	1.5	1.4	0.22	0.20
	60–69[b]	1997/99	2.2	2010[c]	1.10	2.0	1.8	0.29	0.26
PCB 153	7–14[a]	2003/06	0.4						
	18–19[b]	1997/99	0.6	2010[c]	0.20	0.36	0.33	0.052	0.048
	20–29[b]	1997/99	0.9	2010[c]	0.30	0.54	0.50	0.078	0.071
	30–39[b]	1997/99	1.6	2010[c]	0.80	1.5	1.3	0.21	0.19
	40–49[b]	1997/99	2.2	2010[c]	1.10	2.0	1.8	0.29	0.26
	50–59[b]	1997/99	2.8	2010[c]	1.40	2.5	2.3	0.36	0.33
	60–69[b]	1997/99	3.3	2010[c]	1.65	3.0	2.8	0.43	0.39
PCB 180	7–14[a]	2003/06	0.3						
	18–19[b]	1997/99	0.3	2010[c]	0.10	0.18	0.17	0.026	0.024
	20–29[b]	1997/99	0.6	2010[c]	0.20	0.36	0.33	0.052	0.048
	30–39[b]	1997/99	1	2010[c]	0.50	0.91	0.83	0.13	0.12
	40–49[b]	1997/99	1.6	2010[c]	0.80	1.5	1.3	0.21	0.19
	50–59[b]	1997/99	2.1	2010[c]	1.05	1.9	1.8	0.27	0.25
	60–69[b]	1997/99	2.4	2010[c]	1.2	2.2	2.0	0.31	0.29
$\sum$ PCB (138 + 153 + 180)	7–14[a]	2003/06	1						
	18–19[b]	1997/99	1.1	2010[c]	0.37	0.67	0.61	0.10	0.087
	20–29[b]	1997/99	2	2010[c]	0.67	1.2	1.1	0.17	0.16
	30–39[b]	1997/99	3,2	2010[c]	1.6	2.9	2.7	0.42	0.38
	40–49[b]	1997/99	5.1	2010[c]	2.6	4.6	4.3	0.66	0.61
	50–59[b]	1997/99	6.4	2010[c]	3.2	5.8	5.3	0.83	0.76
	60–69[b]	1997/99	7.8	2010[c]	3.9	7.1	6.5	1.0	0.93

[a] Source of data: German Environmental Survey for Children 2003/06.
[b] Source of data: German Environmental Survey 1997/99.
[c] Source of data: German environmental specimen bank.

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Table 4
Reference values (RV_{95}) for antimony, arsenic, cadmium, lead, mercury, nickel, thallium, platinum, uranium in urine or blood (according to Schulz et al., 2011).

Parameter and matrix	Population group (age range in years)	Study period	RV_{95}[a]
Antimony in urine	Children (3–14)	2003–2006	0.3 µg/l
Arsenic in urine	Children who did not eat fish 48 h prior to sample collection (3–14)	2003–2006	15.0 µg/l
	Adults who did not eat fish 48 h prior to sample collection (18–69)	1997–1999	15.0 µg/l
Cadmium in urine	Non-smoking children (3–14)	2003–2006	0.2 µg/l
	Non-smoking adults (18–69)	1997–1999	0.8 µg/l
Cadmium in blood	Non-smoking children (3–14)	2003–2006	<0.3 µg/l[b]
	Non-smoking adults (18–69)	1997–1999	1.0 µg/l
Lead in blood	Children (3–14)	2003–2006	35 µg/l
	Women (18–69)	1997–1999	70 µg/l
	Men (18–69)	1997–1999	90 µg/l
Mercury in urine	Children without dental amalgam fillings (3–14)	2003–2006	0.4 µg/l
	Adults without dental amalgam fillings (18–69)	1997–1999	1.0 µg/l
Mercury in blood	Children who ate fish ≤ 3 times per month (3–14)	2003–2006	0.8 µg/l
	Adults who ate fish ≤ 3 times per month (18–69)	1997–1999	2.0 µg/l
Nickel in urine	Children (3–14)	2003–2006	4.5 µg/l
	Adults (not a strictly representative sample)	Not specified	3.0 µg/l
Platinum in urine	Adults without dental inlays, crowns or bridge elements made of precious metal (18–69)	1997–1999	0.01 µg/l
Thallium in urine	Children (3–14)	2003–2006	0.6 µg/l
	Adults (20–29)[c]	2000–2008	0.5 µg/l
Uranium in urine	Children (3–14)	2003–2006	0.04 µg/l
	Adults (not a strictly representative sample)	2001–2003	0.03–0.06 µg/l[d]

[a] Uncertainty of analysis must be taken into account.
[b] No reference value, but if there should be analytically reliable and confirmed concentrations of Cd in whole blood above the level of 0.3 µg/l, a special exposure must be expected such as active smoking, i.e.
[c] Data obtained from the German Environmental Specimen Bank (ESB) for human tissues.
[d] This background exposure level should be used for orientation unless data are available from a representative population sample.

Table 5
Reference values (RV95) for chlorophenols in urine of children and adults and pentachlorophenol in serum of adults (according to Schulz et al., 2011).

Parameter	Population group (age range in years)	Study period	RV_{95}[a]
2-Monochlorophenol	Children (3–14)	2003–2006	7.0 µg/l
4-Monochlorophenol	Children (3–14)	2003–2006	15.0 µg/l
	Adults (18–69)	1997–1999	15.0 µg/l
2,4-Dichlorophenol	Children (3–14)	2003–2006	2.0 µg/l
	Adults (18–69)	1997–1999	3.0 µg/l
2,5-Dichlorophenol	Children (3–14)	2003–2006	6.0 µg/l
	Adults (18–69)	1997–1999	20.0 µg/l
2,6-Dichlorophenol	Children (3–14)	2003–2006	<0.3 µg/l[b]
	Adults (18–69 years)	1997–1999	<0.3 µg/l[b]
2,3,4-Trichlorophenol	Children (3–14)	2003–2006	<0.3 µg/l[b]
	Adults (18–69)	1997–1999	<0.3 µg/l[b]
2,4,5-Trichlorophenol	Children (3–14)	2003–2006	0.5 µg/l
	Adults (18–69)	1997–1999	1 µg/l
2,4,6-Trichlorophenol	Children (3–14)	2003–2006	0.7 µg/l
	Adults (18–69)	1997–1999	1.5 µg/l
2,3,4,6-Tetrachlorophenol	Children (3–14)	2003–2006	<0.3 µg/l[b]
	Adults (18–69)	1997–1999	1.0 µg/l
Pentachlorophenol (PCP) in urine	Children (3–14)	2003–2006	2.0 µg/l[b]
	Adults (18–69) living in homes without wood preservatives	1997–1999	5.0 µg/l
PCP in serum	Adults (not a strictly representative sample)	1995–1996	12.0 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] No reference value, but if there are analytically reliable and confirmed concentrations above the mentioned value, a special exposure must be expected.

Table 6
Reference values (RV95) for metabolites of organophosphate insecticides (DMP, DMTP, DMDTP, DEP, DETP) in urine (according to Schulz et al., 2011).

Parameter	Population group (age range in years)	Study period	RV95[a]
DMP	Children (3–14)	2003–2006	75 µg/l
	General population[b]	1998	135 µg/l
DMTP	Children (3–14)	2003–2006	100 µg/l
	General population[b]	1998	160 µg/l
DMDTP	Children (3–14)	2003–2006	10 µg/l
DEP	Children (3–14)	2003–2006	30 µg/l
	General population[b]	1998	16 µg/l
DETP	Children (3–14)	2003–2006	10 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] Not a strictly representative sample; DMP: dimethylphosphate; DMTP: dimethylthiophosphate; DMDTP: dimethyldithiophosphate; DEP: diethylphosphate; DETP: diethylthiophosphate.

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Table 7
Reference values (RV95) for metabolites of pyrethroid insecticides (*cis*-Cl_2CA, *trans*-Cl_2CA, 3-PBA) in urine (according to Schulz et al., 2011).

Parameter	Population group (age range in years)	Study period	RV_{95}[a]
cis-Cl_2CA	Children (3–14)	2003–2006	1 µg/l
	General population[b]	1998	1 µg/l
trans- Cl_2CA	Children (3–14)	2003–2006	2 µg/l
	General population[b]	1998	2 µg/l
3-PBA	Children (3–14)	2003–2006	2 µg/l
	General population[b]	1998	2 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] Not a strictly representative sample; *cis*-Cl_2CA and *trans*-Cl_2CA: *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid; 3-PBA: 3-phenoxybenzoic acid.

Table 8
Reference values (RV95) for metabolites of polycyclic aromatic hydrocarbons in urine of non-smoking children and of non-smoking adults (according to Schulz et al., 2011).

Parameter	Population group (age range in years)	Study period	RV95[a]
1-Hydroxypyrene	Non-smoking children (3–14)	2003–2006	0.5 µg/l
	Non-smoking adults (18–69)	1997–1999	0.5 µg/l
1-Hydroxy-phenanthrene	Non-smoking children (3–14)	2003–2006	0.6 µg/l
2/9-Hydroxy-phenanthrene	Non-smoking children (3–14)	2003–2006	0.4 µg/l
3-Hydroxy-phenanthrene	Non-smoking children (3–14)	2003–2006	0.5 µg/l
4-Hydroxy-phenanthrene	Non-smoking children (3–14)	2003–2006	0.2 µg/l
∑Hydroxy-phenanthrene	Non-smoking children (3–14)	2003–2006	1.5 µg/l

[a]Uncertainty of analysis must be taken into account.

Table 9
Reference values (RV_{95}) for hexachlorocyclohexane (HCH) and hexachlorobenzene (HCB) in whole blood of children and adults (according to Schulz et al., 2011, slightly modified).

Parameter	Population group (age range in years)	Study period	RV95[a]
α-HCH	7–14	2003–2006	<0.1 µg/l[b]
	18–69	1997–1999	<0.1 µg/l[b]
β-HCH	7–14	2003–2006	0.1 µg/l
	18–19	1997–1999	0.3 µg/l
	20–29	1997–1999	0.3 µg/l
	30–39	1997–1999	0.3 µg/l
	40–49	1997–1999	0.3 µg/l
	50–59	1997–1999	0.5 µg/l
	60–69	1997–1999	0.9 µg/l
HCB	7–14	2003–2006	0.2 µg/l
	18–19	1997–1999	0.4 µg/l
	20–29	1997–1999	0.5 µg/l
	30–39	1997–1999	1.0 µg/l
	40–49	1997–1999	2.5 µg/l
	50–59	1997–1999	3.3 µg/l
	60–69	1997–1999	5.8 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] No reference value, but if there should be analytically reliable and confirmed concentrations above the mentioned value, a special exposure must be expected.

Table 10
Reference values (RV95) for 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE) in whole blood of children and adults (according to Schulz et al., 2011).

Parameter	Population group (age range in years)	Study period	RV95[a]
DDE	7–14 (West Germany)	2003–2006	0.7 µg/l
	7–14 (East Germany)	2003–2006	1.4 µg/l
	18–19 (West Germany)	1997–1999	1.5 µg/l
	18–19 (East Germany)	1997–1999	3 µg/l[b]
	20–29 (West Germany)	1997–1999	2 µg/l
	20–29 (East Germany)	1997–1999	5 µg/l
	30–39 (West Germany)	1997–1999	4 µg/l
	30–39 (East Germany)	1997–1999	11 µg/l
	40–49 (West Germany)	1997–1999	7 µg/l
	40–49 (East Germany)	1997–1999	18 µg/l
	50–59 (West Germany)	1997–1999	8 µg/l
	50–59 (East Germany)	1997–1999	31 µg/l
	60–69 (West Germany)	1997–1999	11 µg/l
	60–69 (East Germany)	1997–1999	31 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] Based on the 95th percentile of the values from 28 subjects.

20 and 30 years. The measurements are assigned to the years of 1995–2012.

Furthermore the HBM Commission updated the reference values for polychlorinated biphenyls (PCB) in blood of the German population (Table 3, Kommission HBM, 2012, 2016d). This was necessary because the analysis of the time trend of PCB uptake via food – the main exposure route for the general population – shows a marked decrease for Germany. It could therefore be assumed that PCB body burdens have fallen. As current survey data representative of the population are not available, the HBM Commission considered whether data from the analysis of samples from the German environmental specimen bank could be used for a provisional update. It concluded that the dataset from the German environmental specimen bank is suitable, at least for the age group of 20–29, for estimating the change in blood PCB levels over time and the influence of exposure history and age. For the people aged 20–29 the HBM Commission sees a decrease in PCB concentrations in plasma (congeners 138, 153, 180) to about a third (factor of 0.33) in the period 1997–2010. The HBM Commission assumes that the reduction is lower for older persons with a longer exposure history (factor of about 0.5). The assumption of a smaller reduction in blood PCB levels among older age groups from the age of 30 years onwards is based on the fact that the PCB congeners considered have half- lives in plasma of about 10 years and that the longer exposure history of these age groups, particularly the higher rate of uptake during high-contamination years, results in a higher body burden. The HBM Commission is aware of the uncertainties associated with deriving the new PCB reference values through a factor-based estimation. It sees the limited representativeness of the data additionally included and the weaknesses of using modelling. Nevertheless, based on a review of the current data situation (Hardell et al., 2010) in conjunction with an analysis of time trends of data from cross-sectional studies (Ritter et al., 2009, 2011; Quinn et al., 2011; Quinn and Wania, 2012; Schettgen et al., 2011, 2015; Fromme et al., 2015) it considers it justified to lower the reference values.

Table 3 lists the original RV95 values from 1997/99 together with the recalculated provisional RV95 values for PCB concen-

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Table 11
Reference values (RV95) for aromatic amines in urine of non-smoking adults (according to Schulz et al., 2011).

Parameter	Population group	Study period	RV_{95}[a]
Aniline	Non-smoking adults[b]	2003–2004	14.5 µg/l
o-Toluidine	Non-smoking adults[b]	2003–2004	0.20 µg/l
m-Toluidine	Non-smoking adults[b]	2003–2004	0.25 µg/l
p-Toluidine	Non-smoking adults[b]	2003–2004	1.25 µg/l
o-Anisidine	Non-smoking adults[b]	2003–2004	1.10 µg/l
3-Chloroaniline	Non-smoking adults[b]	2003–2004	0.25 µg/l
4-Chloroaniline	Non-smoking adults[b]	2003–2004	1.00 µg/l
3,4-Dichloroaniline	Non-smoking adults[b]	2003–2004	0.45 µg/l
3,5-Dichloroaniline	Non-smoking adults[b]	2003–2004	4.30 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] Not a strictly representative sample.

Table 12
Reference values (RV95) for metabolites of phthalates in urine of children and adults (according to Schulz et al., 2011).

Phthalate	Metabolite(s) in urine	Population group (age range in years)	Study period	RV95[a]
DnBP	MnBP	Children (3–14)	2003–2006	300 µg/l
		Adults (20–29)[b]	2006/2008	70 µg/l
DiBP	MiBP	Children (3–14)	2003–2006	300 µg/l
		Adults (20–29)[b]	2006/2008	140 µg/l
BBzP	MBzP	Children (3–14)	2003–2006	75 µg/l
		Adults (20–29)[b]	2006/2008	15 µg/l
DEHP	5-OH-MEHP + 5-oxo-MEHP	Children (3–14)	2003–2006	280 µg/l
		Adults (20–29)[b]	2006/2008	50 µg/l
DEHP	5-OH-MEHP	Children (3–14)	2003–2006	160 µg/l
		Adults (20–29)[b]	2006/2008	30 µg/l
DEHP	5-oxo-MEHP	Children (3–14)	2003–2006	120 µg/l
		Adults (20–29)[b]	2006/2008	20 µg/l
DEHP	5-cx-MEPP	Children (3–14)	2003–2006	200 µg/l
		Adults (20–29)[b]	2006/2008	30 µg/l
DiNP	Sum of 3 metabolites of DiNP	Children (3–14)	2003–2006	140 µg/l
		Adults (20–29)[b]	2006/2008	60 µg/l
DiNP	OH-MiNP	Children (3–14)	2003–2006	50 µg/l
		Adults (20–29)[b]	2006/2008	20 µg/l
DiNP	oxo-MiNP	Children (3–14)	2003–2006	30 µg/l
		Adults (20–29)[b]	2006/2008	15 µg/l
DiNP	cx-MiNP	Children (3–14)	2003–2006	60 µg/l
		Adults (20–29)[b]	2006/2008	25 µg/l

DnBP: di-*n*-butyl phthalate; MnBP: mono-*n*-butyl phthalate; DiBP: di-isobutyl phthalate; MiBP: monoisobutyl phthalate; BBzP: butyl benzyl phthalate; MBzP: monobenzyl phthalate; DEHP: di(2- ethylhexyl) 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; DiNP: diisononyl phthalate; MiNP: monoisononyl phthalate; OH-MiNP: monohydroxyisononyl phthalate; oxo-MiNP: monooxoisononyl phthalate; cx-MiNP: monocarboxylisononyl phthalate.
[a] Uncertainty of analysis must be taken into account.
[b] Münster, Germany.

Table 13
Reference values (RV95) for perfuorinated compounds in human plasma (according to Schulz et al., 2011).

Parameter	Population group (age range)	Years of the study	RV95[a]
PFOA	Women, men and children < 10 years[b]	2003–2007	10 µg/l
PFOS	Women[b]	2003–2007	20 µg/l
	Men[b]	2003–2007	25 µg/l
	Children < 10 years[b]	2003–2007	10 µg/l

[a] Uncertainty of analysis must be taken into account.
[b] Not a strictly representative sample; PFOA: perfluorooctanoate; PFOS: perfluorooctanesulfonate.

trations in whole blood, plasma and related to the blood lipid level. The new reference values reflect the trend of reduced PCB exposure seen in different datasets. The RV95 values for children aged 7–14 were determined on the basis of data collected in the German Environmental Survey for Children from 2003 to 2006. The HBM Commission considers these to be sufficiently up to date.

Reference values given in Tables 4–13 have been established earlier. They are presented to give a complete overview about all available reference values.

6. Future prospects

For the perfluorinated compounds and other substances a revision of the reference values is necessary. Further data on the exposure of children to diverse chemical substances are currently collected in the context of the German Environmental Survey 2014–2017, GerES V. They will serve as a basis for an actualisation of the reference values for the age group of 3–17 years in the first instance. Concerning the derivation of new HBM values one focus of the Commission's future work will be on the non phthalate plasticisers and other health relevant substances with a high potential for an increased exposure of the general population and/or with a particular toxicological profile. Additionally the cumulative risk

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assessment will play a major role for the work of the HBM Commission.

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