Supplementary material to the publication ”How to use human biomonitoring in chemical risk assessment: Methodological aspects, recommendations, and lessons learned from HBM4EU”

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Supplementary table 1. HBM and current RA guidance used by authorities in the EU (reviewed in (Louro et al., 2019))

Regulatory body, legislation	Name of the guidance document	Notes	Reference
ECHA, Biocides	Guidance on the Biocidal Products Regulation, Volume III, Human Health - Assessment & Evaluation (Parts B+C), ECHA 2017	Short descriptions on the use of HBM is included. Would require further, more detailed guidance.	(Ghazi, 2015)
ECHA, REACH	Chapter R.8 of the IR & CSA guidance: Characterisation of dose [concentration]-response for human health, particularly chapters R.8.1.2.7 Units and Appendix R.8-5 Derivation of DNELs using biomonitoring data	Although this guidance provides examples on the derivation of biomarker-DNELs, they have not been often derived and there may be uncertainties e.g., related to the robustness of the biomonitoring data; whether the available data is robust enough for the setting of biomarker DNEL.	(ECHA, 2012)
ECHA, REACH/OSH	Appendix to Chapter R.8 of the IR & CSA guidance: Guidance for preparing a scientific report for health-based exposure limits at the workplace.	Short descriptions on the setting of the biological limit and guidance values for occupational exposure. Would require further, more detailed guidance.	(ECHA, 2019)
ECHA, REACH	Chapter R.14 of the IR & CSA guidance: Occupational exposure assessment, particularly chapter R.14.6.4.4 Biological monitoring data	Small amount of information on the use of biomonitoring to support occupational exposure assessment. Would require further, more detailed guidance.	(ECHA, 2016a)
ECHA, REACH	Chapter R.15 of the IR & CSA guidance: Consumer exposure assessment	Biomonitoring is mentioned only once at the end of chapter R.15.5.4. Measurements. In addition, Appendix R.15.2 lists valuable sources on exposure data. Would require further, more detailed guidance.	(ECHA, 2016b)
EFSA, Pesticides	Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety	Review of HBM for chemical substances and its application to human exposure assessment for food safety.	(Choi et al., 2015)
	Human biomonitoring data collection from occupational exposure to pesticides	Includes recommendations on the implementation of HBM as part of the occupational health surveillance for pesticides in Europe.	(Bevan et al., 2017)

SCCS, Cosmetics	SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation - 11th revision	Human biomonitoring is included in section 3-3.5.6. However, HBM data is considered mainly as supporting/ complementary information.	(SCCS, 2021)
SCOEL	Methodology for derivation of occupational exposure limits of chemical agents - The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits	Short descriptions on the setting of the biological limit and guidance values for occupational exposure. Would require further, more detailed guidance.	(SCOEL, 2018)
UN FAO	Guidelines on the application of risk assessment for feed	Short descriptions on the use of HBM is included. Would require further, more detailed guidance.	(FAO, 2013)
WHO	Biomarkers and risk assessment: concepts and principles (EHC 155) Human exposure assessment (EHC 214) Biomarkers in risk assessment: validity and validation (EHC 222)	WHO guidance on exposure assessment and the use of HBM in RA. Many ECHA and EFSA principles on the use of HBM are based on these WHO documents.	(WHO and IPCS, 1993) (MacIntosh et al., 2000) (WHO and IPCS, 2001)

Supplementary table 2. Examples of health-based guidance or limit values for the internal exposure available (non-exhaustive)[1]

HBM value Responsible body	Population groups covered	Description of the values and how they are derived	Reference
AOEL and AEL values EFSA and ECHA	operators, workers, bystanders, residents	Active ingredients in pesticides and biocides values are established by EFSA (AOEL) or ECHA (AEL), after proposals made by and consultation with member state experts. They can be set also as internal health-based guidance values to cover all exposure routes. Point of departures are mostly obtained from short- or mid-term toxicological studies but NOAELs or BMDLs corrected for oral absorption if below or equal to 80%.	(EFSA, 2012)
BAT, BLW and EKA values German Committee for the determination of occupational exposure limits (MAK-Commission)	workers	MAK Commission derives three types of biomonitoring values based on epidemiological or toxicological data. Fully health-based values, considered to be protective from the adverse health effects in occupational exposure, are called Biological Tolerance values (Biologische Arbeitsstoff-Toleranzwerte, BAT values). Biological Guidance Values (Biologische Leit-Werte, BLW) can be derived from non-carcinogenic effects of carcinogenic substances and for substances without sufficient data. EKA levels are exposure equivalents for carcinogenic agents	(DFG, 2019)
BE values Summit Toxicology (USA), Health Canada	general population	BEs (biomonitoring equivalents), published as peer-reviewed journal publications, correspond to external limit values set by authorities, e.g., TDIs or RfDs. The publications include a description of how the BE values were derived and therefore, they can be easily modified, if necessary, when external limit values change.	(Angerer et al., 2011; Hays and Aylward, 2009; Hays et al., 2008; Health Canada, 2016)
BEI values American Conference of Governmental Industrial Hygienists (ACGIH)	workers	BEIs are derived for the occupational population. They represent the levels of chemicals which are observed in samples of healthy workers exposed at the TLV level and do not cause adverse health effects. There are also BEIs for chemicals causing non-systemic effects. BEIs are developed by a committee consensus after an evaluation process of peer-reviewed published data.	(ACGIH, 2022)

[1] Up-to-Date list of available biomonitoring guidance values for the general population can be found from the ISES i-HBM Working Group: Human Biomonitoring Health-Based Guidance Value (HB2GV) Dashboard, available at: https://www.intlexposurescience.org/i-hbm/

BLV values, EU Previously the Scientific Committee on Occupational Exposure Limits (SCOEL), set up by the European Commission. Currently (since 2019) ECHA Risk assessment committee (RAC)	workers	BLVs are health-based values meant to be applied at workplaces. BLVs typically correspond to an occupational exposure limit value (OEL) for a given substance. The values can be found in the respective SCOEL/RAC OEL recommendations. Until now, only the BLV for Lead (Pb) has been included in the EU Chemical Agents Directive (98/24/EC), the other values are only recommendations from SCOEL/RAC.	SCOEL document library: https://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684 RAC OEL recommendations: https://echa.europa.eu/en/oels-activity-list
BLV values ANSES, France	workers	ANSES BLVs are national values derived for the occupational population. ANSES BLVs are derived for relevant chemicals if routes other than inhalation contribute largely to absorption and for cumulative pollutants, to take into account interindividual factors. (ANSES 2021). BLVs can be derived for substances with or without a threshold effect.	https://www.anses.fr/en/content/biological-limit-values-chemicals-used-workplace
$DNEL_{biomarker}$ ECHA/RAC, REACH registrants	general population and workers	If applicable data are available, $DNEL_{biomarker}$ values can be derived by REACH registrants, although not many have been set so far. Some $DNEL_{biomarkers}$ have been derived by ECHA/RAC as part of the restriction process, for example a for n-methylpyrrolidone (NMP)	(ECHA, 2012)
HBM-I and II values German HBM Commission at German Environment Agency (Umweltbundesamt – UBA)	general population	HBM-I and II values are derived toxicologically and/or epidemiologically. The HBM-I value represents the concentration of a substance in human biological material at and below which, according to the knowledge and judgement of the HBM Commission, there is no risk for adverse health effects and, consequently, no need for action. The HBM-II value represents the concentration of a substance in human biological material at and above which, according to the knowledge and judgement of the HBM Commission, there is an increased risk for adverse health effects. Consequently, there is an immediate need for exposure reduction measures and the provision of biomedical advice.	(Apel et al., 2017)
HBM-GVs HBM4EU	general population and workers	HBM-GVs have been derived within the HBM4EU consortium for the general and occupational populations, depending on the substance. A jointly agreed strategy was followed, and depending on data availability, the values are based on epidemiological data, toxicity reference values, or PODs from animal studies. Each value derivation was subjected to a consultation process before adoption. The HBM-GV for the general population is defined as the concentration of a substance or its specific metabolite(s) in human biological material at and below which, according to current	(Apel et al., 2020)

	knowledge, there is no risk of health impairment anticipated. Thus, this value is equivalent to the HBM-I value of the German Human Biomonitoring Commission. The HBM-GV for occupationally exposed adults is defined as the concentration of a substance or its relevant metabolite(s) in human biological material aiming to protect workers exposed to the respective substance regularly (each workday), and over the course of a working life from the adverse effects related to medium- and long-term exposure.

Supplementary table 3. Common challenges related to evaluation of representativeness and applicability of occupational biomonitoring data for risk assessment

Challenge	Response
Missing data for contextual information on operational conditions and risk management measures (RMMs) implemented	This is a frequent issue in occupational studies. The relevance of this issue is dependent on the amount of missing data for operational conditions and RMMs (no data or only a few datapoints). When available, the dataset may provide valuable data to identify which RMMs are more effective. Even in case of limited contextual data HBM dataset can be considered at least as supplementary data to support modelling or external exposure data. This applies especially to large datasets.
What should be considered for defining the sampling strategy?	Previous knowledge of toxicokinetic and workplace/tasks characteristics is fundamental for defining the sampling strategy. The more extensive this knowledge is, the better the sampling can be defined and less assumptions will be needed for risk assessment. Altogether these data will allow defining an adequate sampling strategy, considering: - Pre- and post-shift sample collection – useful to attribute exposure to occupational context and differentiate between tasks and exposure scenarios (e.g., food and tobacco consumption, air pollution) - Half-life of chemicals and/or metabolites – as mentioned above, it is very important to consider this aspect, since it will determine what is the best timeframe for sample collection (e.g., immediately after the shift, next morning and/or end of the working week). In the case of long half-life chemicals (e.g., Pb), the sampling time might not be relevant. - Workplace/task characteristics and representativity – it is important to know in detail the tasks performed and the workplace conditions to identify what will be the potential sources of exposure and moments/tasks that will probably imply exposure (e.g., which tasks implicate the use/exposure to the substance being evaluated). In addition, especially in case of short half-life chemicals it needs to be ensured that the day the sample has been taken represents a typical workday. - Exposure peaks – in line with the previous points, these peaks should be identified and considered when designing the sample collection, gathering data from workplace and substance' toxicokinetic. These might be particular tasks that imply higher exposure due for instance to the amount of the substance used and/or the conditions for the development of those tasks (e.g., lack of local exhaust ventilation, confined spaces)
Background exposure (from sources other than occupational context)	Availability of the information on background exposure in the country/area. This might represent information from general population studies or from a specific occupationally non-exposed cohort. If there is a possibility that there might be e.g., country differences in the background exposure of the general population, the background data should preferably represent the given area. Research studies typically include a specific control group. This may include workers performing administrative tasks in a company or workers from a different company/sector. If controls are recruited from the same company, it needs to be checked that indirect exposure does not occur in the company/companies enrolled in the study. Pre-shift samples (in Monday morning after weekend) might also provide useful information on the background exposure levels but only in case of short half-life chemicals without any accumulation in the body. Even some substances with short half-life from

	blood may show extended excretion in the urine e.g., due to slow dermal or lung absorption.
Similar Exposure Group considerations	This allows to identify group of workers (with similar exposure profiles, meaning similarity and frequency of the tasks performed, the materials and processes with which they work, and the similarity of the way they perform the tasks and RMMs available) with higher exposure and risk and where additional RMMs need to be implemented first.
Added value of HBM data when compared with industrial hygiene monitoring data (e.g., air, dermal, surfaces). What HBM data can add and how does it complement the industrial hygiene data?	HBM provides results for aggregated exposures, i.e., considering all possible routes (inhalation, ingestion, dermal absorption). This represents an enormous added value compared to other methods because the overall exposure is determined. However, it should be referred that using only HBM data makes it more difficult to identify the exposure route contributing more for the overall exposure and that should be targeted for the additional RMMs. Here, the collection of contextual data supports the interpretation of HBM and industrial hygiene data (e.g., air monitoring, dermal wipe samples) the identification of the relevant exposure route(s) and the effectiveness of the RMMs in place.
Results below LOD/LOQ	The analytical methods selected for samples' analysis should be fit for purpose, i.e., with performance parameters that are adequate for analysis of the predicted levels of exposure, matrices, and substances. Especially in case of CRM substances it needs to be ensured that LOQs are low enough (preferably LOQs being ≤10% of the biological guidance or limit values)
Selection bias	This is common challenge in case of all occupational exposure data and therefore not specific to HBM data. Most poorly performing workplaces might not be willing to participate monitoring campaigns and the better performing companies are over-represented in the dataset. If the aim is to gather representative data from the given industry field attention should be paid on the recruitment of the participants to minimize the impact of the selection bias.

Sources of pre-analytical and analytical uncertainties

Supplementary table 4. Issues to be considered in pre-analytical and analytical phase (see text for details)

Pre-analytical phase	Specific notes
Sample contamination and use of non-contaminated materials	Especially important when parent compound is analysed. In occupational context, especially samples for metal analyses need careful control of contamination.
	Materials used should be pre-tested for impurities.
Sample type and sample collection time	First morning void, morning, post-shift (in occupational settings) spot sample or 24-h urine sample.
	Especially important for short-lived chemicals in occupational settings.
Sample stability during transportation and storage	Especially important for chemicals with limited lifespan in biological matrixes, for example volatile substances.
Urinary dilution	Very dilute urine samples should be applied with caution.
	Creatinine adjustment or specific gravity adjustment typically applied to control this.
Analytical phase	**Specific notes**
Sample analyses should be carried out by a laboratory which passed high quality QA/QC or by an accredited laboratory.	Accreditation guarantee that appropriate quality assurance procedures are applied.
State-of-art analytical instrumentation and methods should be used whenever possible.	
Sensitivity and specificity of the method used for the given substance and sample matrix should be reported.	The limit of quantification (LOQ) should be low enough to quantify the substance in adequate percentage of the samples.

Pre-analytical phase

When using HBM data for the risk assessment purposes, it is important to note most errors in analytical testing occur before any analysis has been performed (see e.g., (Bonini et al., 2002; Plebani, 2006). In order to minimize errors in pre-analytical part it is important to pay special attention to sampling materials, sample collection, sample processing after collection, sample stability during transportation to the analytical laboratory, and sample processing once received in the laboratory (WHO, 1996) (Supplementary table 4). In HBM4EU, errors and variability caused by sampling phase has been minimised by creating detailed SOPs for the sampling (Esteban López and Castaño, 2018).

In case of occupational trace metal analysis, sample contamination is one of the main sources of error. Contamination may be derived from the sample collection vessels and materials, from the clothes and skin of the subject or the sample collector, from the air, and from the chemicals added to the sample (e.g., preservatives, anti-coagulants). Thus, only special vessels and tubes suitable for the given sampling purpose should be used, and they should be of an appropriate purity. Contamination of hands and clothes is an issue especially in occupational biomonitoring and may often explain the outliers (extremely high levels in some samples) in the dataset. Sample contamination is usually not an issue when metabolite is being analysed.

Concentrations of some chemicals in body fluids are often not constant but may vary with time. Differences in sample collection time may explain some variability between datasets. Especially in occupational biomonitoring exposure, sample collection time is very critical. Chemicals with elimination half-life of some hours (e.g., many organic solvents, phthalates, bisphenols) are rapidly cleared from the body. Thus, sample collection should be carried out right after the exposure ends (in occupational exposure assessment the sampling time is post-shift). Sample collection time is not as critical for chemicals with long half-life (e.g., cadmium, lead, PCBs, PFOA, PFAS).

Stability of HBM samples might be affected during the storage and transportation. Some organic chemicals have limited lifespan in biological matrixes (WHO, 1996). Accordingly, sample transportation should be carried out according to the instructions given by the analytical laboratory. Samples should be stored in appropriate vessels/tubes resistant to variations in temperature and humidity, and to physical impacts (e.g., dropping on the floor). One should verify that the sample is properly packed to stay stable during the sample transportation (including mailing). Long shipment times should be avoided especially when the sample stability is of concern. If analysis is not carried out immediately after sample is received in the laboratory, appropriate storage conditions should be arranged in the laboratory.

Urinary dilution is one source of variation (see below). Accordingly, passing of urine should preferably be avoided, for example, within three hours before collecting the void. Also, excessive consumption of beverages should be avoided before the sampling.

Urine concentration can vary widely due to changes in fluid intakes and fluid losses through sweating. Although collection of 24-h urinary volume is the most appropriate sample, due to practical reasons spot urine samples are typically collected. When chemical concentration is dependent on urine production levels, it is often reported either relative to urinary creatinine concentration to correct for variable dilutions in spot samples (creatinine adjustment/correction) or normalized to a certain average urine specific gravity (relative density). The creatinine adjustment method is more often used although it is known that the production of creatinine reflects muscle mass, which in part leads, e.g., to gender and age differences in creatinine concentrations. Creatinine adjustment is an appropriate method when the analyte and creatinine are excreted in the similar rate. Another method – although less frequently used – is normalization to a specific gravity (SG). Recent study even suggests applying urinary dilution correction based on SG (Sauve et al., 2015). SG method has also an advantage that the unit stays the same as of the original, non-normalized result. However, since there is no agreement in the scientific community whether correction for creatinine or specific gravity should be applied for certain chemicals, there might be three types of HBM data available in the literature: non-corrected, creatinine adjusted and SG normalized data.

It is generally accepted that very dilute or very concentrated urine samples are usually not suitable for HBM. Some organisations have proposed 'acceptable creatinine and specific gravity ranges' for HBM. According to the World Health Organisation (WHO) urine specimens should have a creatinine concentration of >0.3 g/l (3 mmol/l) and <3.0 g/l (26.5 mmol/l) or a specific gravity of >1.010 and <1.030. Specimens falling outside of these ranges should be discarded, as it is unlikely that any correction will give accurate results (WHO, 1996). ACGIH has adopted the same ranges (ACGIH, 2022). IRSST proposed same upper limit for creatinine and SG as WHO and ACGIH but suggested 0.5 g/l (4.4 mmol/l) for the lower creatinine limit (SG 1.010) (Gagné, 2019). On the other hand, DFG applied the same lower limit as IRSST but proposed upper limit of 2.5 g/l (22.1 mmol/l) for creatinine and 1.024 for SG (Weihrauch et al., 2012).

A common recommendation in HBM is to discard the urine sample if it falls outside the 'acceptable range', and flag the result as 'dilute', 'low/high creatinine or SG', 'sample integrity failed', etc. In some cases, this is an appropriate recommendation especially when it is possible to request a new urine sample. Unfortunately, especially in population studies it is often not possible to collect a new urine specimen. Accordingly, various practices have been applied for how to treat dilute and concentrated urine specimen. Also, in many studies and reports no information is given for urinary dilution. It can be speculated that few specimens falling outside the 'acceptable range' do not necessarily question the results in case of large study groups (i.e., high number of samples). But in case of very small study group (low number of samples) even few specimens falling outside the 'acceptable range' might cause uncertainty to the results. Nevertheless, the urinary results outside the 'acceptable range' should always be applied with caution. It is recommended to pay attention how the urinary results are reported, how the urinary dilution has been taken into consideration, and how the specimen falling outside the 'acceptable range' have been dealt with.

Creatinine adjustment (and specific gravity normalization) can have a substantial effect on the HBM results in an individual level. In a group level, especially with very large study groups, the effect is less prominent. Although adjusted/normalized HBM data are recommendable over data without any dilution corrections, lack of correction does not preclude the use of HBM data for risk assessment purposes.

Analytical phase

Essential part of the HBM campaign is that all sample analyses are carried out by an accredited laboratory or a laboratory which successfully passed demanding QA/QC measures such as those of HBM4EU whenever possible (Esteban Lopez et al., 2021). Accreditation and certification require quality control, which means that accredited laboratories must use appropriate quality assurance procedures. This means undertaking of internal quality assurance (e.g., frequent audits, replicate analysis, use of certified reference materials) and successful performance in external quality control schemes where available. The level of quality control should be reported in the publications and reports. New analytical methods or methods currently developed are not necessarily accredited yet but also here appropriate quality control should be applied when possible, and quality assurance procedures should be reported.

It is recommended to use the state-of-art analytical instrumentation for the analysis. In the present-day HBM this means, e.g., LC-MS/MS, GC-MS/MS, GC-HRMS. Despite the analytical instrumentation used, the laboratory carrying out HBM analysis should always report the sensitivity of the method used for the given substance and sample matrix, preferably in the form of the limit of quantification (LOQ[2]). The LOQ should be low enough to quantify the substance in adequate percentage of the samples. It should be noted that the LOQ may vary even between analytical series carried out in the same laboratory. Accordingly, the LOQ must be regularly verified. Note that there are differences in LOQs between laboratories – sometimes even substantial differences. When analytical method is adopted from the literature, no literature LOQs should be applied but the LOQ should always be determined in the laboratory carrying out the actual analysis. There are various methods to define the LOQ, which means that it is highly recommended to report the given method.

[2] LOQ is the lowest possible concentration of the analyte that can be quantified by the method in a reliable way. Reliable means that a suitable precision and trueness must exist and must also be demonstrated. LOQ is higher than the limit of detection (LOD). The LOD is the lowest possible concentration of the chemical that can be detected (but not quantified) with certain degree of confidence. Although LOQ is recommended parameter to report the performance of the analytical method in quantitative analysis, it is acceptable to report the LOD. In this case it is also advisable to report how the LOD was derived. If no LOQ/LOD is reported, the data should be used with caution.

Supplementary table 5. Unit conversion examples for human biomonitoring data

From	To	Conversion	Example conversion for Bisphenol A**
µg/l	µmol/l	÷ MW	÷ 228.3
µmol/l	µg/l	× MW	× 228.3
µg/l	nmol/l	× 1000 ÷ MW	× 1000 ÷ 228.3
nmol/l	µg/l	× MW ÷ 1000	× 228.3 ÷ 1000
µg/l	µg/g creatinine*	× 1 / a	× 0.74
µg/l	µmol/mol creatinine*	÷ MW × 1 / b	÷ 228.3 × 83
µg/g creatinine	µmol/mol creatinine	÷ MW × 113.1	÷ 228.3 × 113.1
µmol/mol creatinine	µg/l*	× MW ÷ 1 / b	× 228.3 ÷ 83

MW = Molecular Weight (g/mol); a = mean urinary creatinine concentration in g/l; b = mean urinary creatinine concentration in mol/l; MW of creatinine = 113.1 g/mol.

* = Rough approximations. Note that these approximations can assist with converting published data but should not be used for direct numerical conversion in reporting data. In the latter case the creatinine concentration must be measured in the laboratory.

** Example: Bisphenol A, MW 228.3 g/mol, 1 litre of urine contains approximately 1.36 g of creatinine (equivalent to 12.02 mmol/l creatinine) (Cocker et al., 2011). Note that also other mean/median creatinine values have been proposed – typically they vary between 1.0 and 1.6 g/l (ACGIH, 2022; Bader et al., 2013; Weihrauch et al., 2012).

Supplementary table 6. List of recognized advantages and limitations on the use of effect biomarkers for risk assessment

Advantages	Limitations and uncertainties
Identify early biological effects before disease development	Lack of specificity in relation to a specific substance
Integrating multiple sources and routes of exposure	Some allow a direct interpretation in terms of risk at an individual level, but others provide information that can only be interpreted at the population level
Some can be determined in specimens collected using non-invasive methods (urine, exfoliated buccal cells, saliva)	For many, reference or guidance levels are not available
Contributing to mechanistic insights leading to AOPs establishment	Low number of studies using effect biomarkers measurement limits comparability
Reflecting the combined effects of Mixtures exposure	Often affected by lifestyle factors, e.g., smoking, diet and high (natural) background variation that have to be taken into account
Identify susceptible individuals in a population	Privacy issues, particularly sensitive if studying susceptible individuals
Contribute to identify subgroups at a higher risk, e.g., in occupational settings	
Together with exposure biomarkers, contribute to link exposure to health outcome	

List of abbreviations used in the paper

1-OHPyr	1-hydroxy-pyrene
2,4/2,6-TDI	toluene diisocyanate
3-PBA	3-phenoxybenzoic acid
4-FPBA	4-fluoro-3-phenoxybenzoic acid
AAMA	acrylamide mercapturic acid
AChE	acetylcholinesterase
ADI	acceptable daily intake
AOP	adverse outcome pathway
AR	attributable risk
As(III)	arsenic ion (oxidation state +3)
As(V)	arsenic ion (oxidation state +5)
ATSDR	Agency for Toxic Substances and Disease Registry
BaA	benzo(a)anthracene
BaP	benzo(a)pyrene
BbF	benzo(b)fluoranthene
BBzP	benzyl butyl phthalate
BCEP	bis(2-chloroethyl) phosphate
BCIPP	bis(1-chloro-2-propyl) phosphate
BDCIPP	bis(1,3-dichloro-2-propyl) phosphate
BE	biomonitoring equivalent
BHR	bronchial hypersensitiveness
BLL	blood lead levels
BLV	biological limit value
BMDL	Benchmark Dose (Lower Confidence Limit)
BP-3	benzo-phenone-3
BPA	bisphenol A
BPS	bisphenol S
Cd	cadmium
CHMS	Canadian Health Measure Survey
CHR	chrysene
CI	confidence interval
ClF3CA	3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid (often also abbreviated CFMP)

Cr(III)	trivalent chromium
Cr(VI)	hexavalent chromium
DALY	disability-adjusted life year
DBCA	3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid
DCCA	3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid
DECOS	Dutch Expert Committee on Occupational Safety
DEHP	bis(2-ethylhexyl) phthalate
DiBP	diisobutyl phthalate
DiNP	diisononyl phthalate
DMA	dimethylarsinic acid
DMF	n,n-dimethyl-formamide
DnBP	di-n-butyl phthalate
DON	deoxynivalenol
EBC	exhaled breath condensate
EBoD	environmental burden of disease
EC	European commission
ECHA	European Chemicals Agency
ECHA-RAC	risk assessment committee at ECHA
EDI	estimated daily intake
EFSA	European Food Safety Authority
ELCR	excess lifetime cancer risk
ESB	German Environmental Specimen Bank
FAO	Food and Agriculture Organization of the United Nations
FIOH	Finnish Institute of Occupational Health
FLEHS	Flemish Environment and Health Study
FSIQ	full-scale IQ points
Fue	fractional urinary excretion
GDPR	General Data Protection Regulation
GenPop	general population
GerES	German Environmental Survey of Children and Adolescents
GM	geometric mean
HB2GV	Human Biomonitoring Health-based Guidance Value Dashboard
HBGV	health-based guidance value
HBM	human Biomonitoring

HBM4EU	European Human Biomonitoring Initiative
HBM-GV	human biomonitoring guidance value derived within the HBM4EU project
HBM-PoD	human biomonitoring points of departure
HDA	hexamethylene diamine, HDI metabolite
HDI	hexamethylene diisocyanate
Hg	mercury
HI	hazard index (approach)
HQ	hazard Quotient
HR	hazard ratio
iAs	inorganic arsenic
ICD	International statistical classification of deseases and related health problems (by WHO)
ICI/EQUAS	HBM4EU interlaboratory comparison and external quality assurance
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MDA	4,4′-methylenedianiline, MDI metabolite
MDI	4,4'-methylene diphenyl diisocyanate
MeHg	methylmercury
MMA	monomethylarsonic acid
MoE	margin of exposure (approach)
MRA	mixture risk assessment
NCO	isocyanate (chemical group)
NEP	1-ethylpyrrolidin-2-one
NHANES	National Health and Nutrition Examination Survey
NMP	1-methyl-pyrrolidin-2-one
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit value
OPFR	organophosphorus flame retardants
OSH	occupational safety and health
o-toluidine	ortho-toluidine
P50	median
P75	75th percentile

P90	90th percentile
P95	95th percentile
PAH4	consists of: BaA, BbF, BaP, CHR
PAHs	polycyclic aromatic hydrocarbons
Pb	lead
PBPK	physiologically based pharmacokinetic (modelling)
PDI	probable daily intake
PFAS	per- and polyfluoroalkyl substance
PFBS	perfluorobutanesulfonic acid
PFDA	perfluorodecanoic acid
PFDoDA	perfluorododecanoic acid (often also abbreviated PFDoA)
PFHpS	perfluoroheptanesulfonic acid
PFHxA	perfluorohexanoic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
PFUnDA	perfluoroundecanoic acid (often also abbreviated PFUnA)
PoD	point of departure
PPP	plant protection products
RA	risk assessment
RAC	Risk assessment committee at ECHA
RBC	red blood cell
RBP	retinol-binding protein
RCR	risk characterisation ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals, Regulation (EC) No 1907/2006
RMMs	risk management measures
RPF	relative potency factor
RQ	risk quotient
RR	relative risk
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
SES	socioeconomic status

SG	specific gravity
TCEP	tris (2-chloroethyl) phosphate
TCIPP	tris (chloropropyl) phosphate
TCPy	3,5,6-trichloro-2-pyridinol
TDA	toluene diamine, metabolite of toluene diisocyanate
TDCIPP	tris (1,3-dichloro-2-propyl) phosphate
TDI	tolerable daily intake
t-TDI	temporary tolerable daily intake
trans-CDCA	trans-chrysanthemum dicarboxylic acid
TWI	tolerable weekly intake
U-	urinary
U-Cr	urinary total chromium
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation
β2M	beta-2-microglobulin

References

ACGIH, 2022. American Conference of Governmental Industrial Hygienists. 2022 TLVs® and BEIs®. Based on the Documentation of the Threshold Limit Values for chemical Substances and Physical Agents & Biological Exposure Indices.

Angerer, J., Aylward, L.L., Hays, S.M., Heinzow, B., Wilhelm, M., 2011. Human biomonitoring assessment values: approaches and data requirements. Int J Hyg Environ Health 214, 348-360. doi:10.1016/j.ijheh.2011.06.002

Apel, P., Angerer, J., Wilhelm, M., Kolossa-Gehring, M., 2017. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health 220, 152-166. doi:10.1016/j.ijheh.2016.09.007

Apel, P., Rousselle, C., Lange, R., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2020. Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J Hyg Environ Health 230, 113622. doi:10.1016/j.ijheh.2020.113622

Bader, M., Messerer, P., Will, W., 2013. Urinary creatinine concentrations in an industrial workforce and comparison with reference values of the general population. Int Arch Occup Environ Health 86, 673-680. doi:10.1007/s00420-012-0802-4

Bevan, R., Brown, T., Matthies, F., Sams, C., Jones, K., Hanlon, J., La Vedrine, M., 2017. Human biomonitoring data collection from occupational exposure to pesticides. EFSA Supporting Publications 14, 1185E. doi:10.2903/sp.efsa.2017.EN-1185

Bonini, P., Plebani, M., Ceriotti, F., Rubboli, F., 2002. Errors in laboratory medicine. Clin Chem 48, 691-698. doi:10.1093/clinchem/48.5.691

Choi, J., Aarøe Mørck, T., Polcher, A., Knudsen, L.E., Joas, A., 2015. Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety. EFSA Supporting Publications 12, 724E. doi:10.2903/sp.efsa.2015.EN-724

Cocker, J., Mason, H.J., Warren, N.D., Cotton, R.J., 2011. Creatinine adjustment of biological monitoring results. Occupational medicine (Oxford, England) 61, 349-353. doi:10.1093/occmed/kqr084

DFG, 2019. Deutsche Forschungsgemeinschaft. List of MAK and BAT Values 2019: Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report 5510.1002/9783527826889. doi:10.1002/9783527826889

ECHA, 2012. Guidance on information requirements and chemical safety assessment – Chapter R.8: Characterisation of dose [concentration]-response for human health. Reference: ECHA-2010-G-19-EN. Available at: https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/.

ECHA, 2016a. Guidance on information requirements and chemical safety assessment : Chapter 14: occupational exposure assessment, version 3.0 - August 2016, European Chemicals Agency. https://data.europa.eu/doi/10.2823/678250.

ECHA, 2016b. Guidance on information requirements and chemical safety assessment : chapter R.15 : consumer exposure assessment, European Chemicals Agency. https://data.europa.eu/doi/10.823/940476.

ECHA, 2019. Appendix to Chapter R.8, guidance for preparing a scientific report for health-based exposure limits at the workplace : guidance on information requirements and chemical safety assessment, European Chemicals Agency. https://data.europa.eu/doi/10.2823/333736.

EFSA, 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 10, 2579. doi:10.2903/j.efsa.2012.2579

Esteban López, M., Castaño, A., 2018. Annex 2.2.3 to HBM4EU D7.3. SOP 3: Procedure for obtaining human samples. doi:10.5281/zenodo.6394202

Esteban Lopez, M., Goen, T., Mol, H., Nubler, S., Haji-Abbas-Zarrabi, K., Koch, H.M., Kasper-Sonnenberg, M., Dvorakova, D., Hajslova, J., Antignac, J.P., Vaccher, V., Elbers, I., Thomsen, C., Vorkamp, K., Pedraza-Diaz, S., Kolossa-Gehring, M., Castano, A., 2021. The European human biomonitoring platform - Design and implementation of a laboratory quality assurance/quality control (QA/QC) programme for selected priority chemicals. Int J Hyg Environ Health 234, 113740. doi:10.1016/j.ijheh.2021.113740

FAO, 2013. Guidelines on the application of risk assessment for feed. CAC/GL 80-2013. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXG%2B80-2013%252FCXG_080e.pdf.

Gagné, S., 2019. Guide de prélèvement des échantillons biologiques, 2nd édition. Guides et outils techniques et de sensibilisation. T-25. Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), Montréal (Québec). https://www.irsst.qc.ca/media/documents/pubirsst/T-25.pdf.

Ghazi, A., 2015. Extended lymph node dissection for intermediate and high-risk prostate cancer: do we have all the evidence? Asian J Androl 17, 335. doi:10.4103/1008-682X.143042

Hays, S.M., Aylward, L.L., 2009. Using Biomonitoring Equivalents to interpret human biomonitoring data in a public health risk context. J Appl Toxicol 29, 275-288. doi:10.1002/jat.1410

Hays, S.M., Aylward, L.L., LaKind, J.S., Bartels, M.J., Barton, H.A., Boogaard, P.J., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Lipscomb, J., Kilpatrick, M.E., Krewski, D., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.M., Viau, C., Yager, J.W., Biomonitoring Equivalents Expert, W., 2008. Guidelines for the derivation of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. Regulatory toxicology and pharmacology : RTP 51, S4-15. doi:10.1016/j.yrtph.2008.05.004

Health Canada, 2016. Biomonitoring Equivalents as a Screening Tool for Population Level Biomonitoring Data: A Health Canada Perspective. https://www.canada.ca/content/dam/hc-sc/documents/services/publications/science-research-data/biomonitoring-equivalents-screening-tool-population-level-data/biomonitoring-equivalents-screening-tool-population-level-data.pdf.

Louro, H., Heinala, M., Bessems, J., Buekers, J., Vermeire, T., Woutersen, M., van Engelen, J., Borges, T., Rousselle, C., Ougier, E., Alvito, P., Martins, C., Assuncao, R., Silva, M.J., Pronk, A., Schaddelee-Scholten, B., Del Carmen Gonzalez, M., de Alba, M., Castano, A., Viegas, S., Humar-Juric, T., Kononenko, L., Lampen, A., Vinggaard, A.M., Schoeters, G., Kolossa-Gehring, M., Santonen, T., 2019. Human biomonitoring in health risk assessment in Europe: Current practices and recommendations for the future. Int J Hyg Environ Health 222, 727-737. doi:10.1016/j.ijheh.2019.05.009

MacIntosh, D.L., Spengler, J.D., WHO, IPCS, 2000. Human exposure assessment. Environmental health criteria 214. Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization; and produced under the framework of the Inter-Organization Programme for the Sound Management of Chemicals. https://apps.who.int/iris/handle/10665/42181, https://inchem.org/documents/ehc/ehc/ehc214.htm. World Health Organization, Geneva.

Plebani, M., 2006. Errors in clinical laboratories or errors in laboratory medicine? Clin Chem Lab Med 44, 750-759. doi:10.1515/CCLM.2006.123

Sauve, J.F., Levesque, M., Huard, M., Drolet, D., Lavoue, J., Tardif, R., Truchon, G., 2015. Creatinine and specific gravity normalization in biological monitoring of occupational exposures. J Occup Environ Hyg 12, 123-129. doi:10.1080/15459624.2014.955179

SCCS, 2021. Scientific Committee on Consumer Safety (SCCS), SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 11th revision, 30-31 March 2021, SCCS/1628/21. https://ec.europa.eu/health/publications/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-11th-revision_en.

SCOEL, 2018. European Commission, Directorate-General for Employment, Social Affairs and Inclusion. Methodology for derivation of occupational exposure limits of chemical agents : the General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL) 2017. Publications Office. https://data.europa.eu/doi/10.2767/435199.

Weihrauch, M., Schulze, B., Schaller, K.H., 2012. Creatinine as a Reference Parameter for the Concentration of Substances in Urine [BAT Value Documentation, 1998], The MAK-Collection for Occupational Health and Safety, pp. 36-44. doi:10.1002/3527600418.bb6027urie0003

WHO, 1996. Biological Monitoring of Chemical Exposure in the Workplace, Guidelines, Volume 1. World Health Organization, Geneva, pp. 20-51.

WHO, IPCS, 1993. World Health Organization and International Programme on Chemical Safety. Biomarkers and risk assessment : concepts and principles. Environmental health criteria 155. Published under the joint sponsorship of the United Nations environment Programme, the International Labour Organisation, and the World Health Organization. https://apps.who.int/iris/handle/10665/39037. World Health Organization, Geneva.

WHO, IPCS, 2001. World Health Organization & International Programme on Chemical Safety. Biomarkers in risk assessment : validity and validation. Environmental health criteria 222. World Health Organization. https://apps.who.int/iris/handle/10665/42363, https://inchem.org/documents/ehc/ehc/ehc222.htm. World Health Organization, Geneva.